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Pulmonary arterial hypertension

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Introduction

Pulmonary arterial hypertension (PAH) is a progressive and life-threatening condition characterized by pulmonary vascular remodeling, leading to increased pulmonary vascular resistance (PVR) and right ventricular (RV) dysfunction. Over the past 30 years, many advances have been made: the hemodynamic definition and risk score assessment have been revised, and new pharmacological agents have been developed, but PAH remains incurable.

The complexity of the disease requires a multidisciplinary approach and regular multiparametric evaluation of patients, with the assessment of the risk of 1-year mortality. The final goal recommended by ESC/ERS guidelines is to achieve and maintain a low-risk profile, ultimately improving survival.

Pathophysiology and therapeutic pathways

PAH results from an imbalance between vasoconstriction and vasodilation, along with cellular proliferation and inflammation. The intricate pathophysiological mechanisms underlying PAH involve multiple signaling pathways, including the prostacyclin, endothelin, and nitric oxide (NO) pathways. These mechanisms contribute to endothelial dysfunction, excessive smooth muscle proliferation, and increased pulmonary arterial pressure. Current therapeutic strategies are designed to modulate these dysregulated pathways, restoring vascular homeostasis and alleviating hemodynamic burden to mitigate RV failure. Although pharmacological interventions can slow disease progression, they do not halt the pathological remodeling process, underscoring the need for continued research into novel treatment modalities that target disease mechanisms more effectively.

Endothelin Receptor Antagonists (ERAs)

Endothelin-1 (ET-1), a potent vasoconstrictor, exerts its effects through ETA and ETB receptors. ET-1 plays a pivotal role in PAH pathogenesis by promoting vasoconstriction, fibrosis, and cellular proliferation. ERAs such as bosentan, macitentan, and ambrisentan counteract ET-1 signaling, improving pulmonary hemodynamics and exercise capacity. Clinical trials, including BREATHE-1, ARIES, and SERAPHIN, have demonstrated significant benefits, such as improved functional class, delayed disease progression, and enhanced quality of life. Given the potential adverse effects related to ERAs, including peripheral edema, hepatotoxicity, and anemia, a careful patient monitoring is required. Moreover, women of childbearing potential treated with ERAs need strict contraceptive measures because of the teratogenic potential of this class of drugs. The long-term benefits of ERAs are well-documented, with macitentan showing superior efficacy in reducing morbidity and mortality in PAH patients.

Phosphodiesterase Type 5 Inhibitors (PDE-5i)

PDE-5 inhibitors, including sildenafil and tadalafil, enhance cyclic guanosine monophosphate (cGMP) signaling to promote vasodilation and reduce PVR. By inhibiting PDE-5, these agents prevent the degradation of cGMP, thereby sustaining the vasodilatory effects of NO. The SUPER and PHIRST trials confirmed their efficacy in improving 6-minute walk distance (6MWD), WHO functional class, and hemodynamic parameters. PDE-5 inhibitors are widely used as first-line therapy for PAH patients in combination with ERAs. Emerging evidence suggests that PDE-5 inhibitors may have additional benefits beyond vasodilation, including potential anti-inflammatory and antiproliferative effects, which could contribute to long-term disease modulation. Side effects are related to vasodilatation and include headache, flushing and dyspepsia.

Soluble Guanylate Cyclase (sGC) Stimulators

Riociguat is a first-in class sGC stimulator, with a dual mode of action. In contrast to PDE-5 inhibitors, it directly stimulates sGC, enhancing cGMP production independently of NO availability. In PATENT-1 Riociguat has been shown to improve exercise capacity and PVR in treatment-naïve and pretreated PAH patients. The RESPITE and REPLACE studies further support its use as an alternative therapy in patients with insufficient response to PDE-5 inhibitors. Due to the unfavorable risk-benefit profile resulted in the PATENT PLUS trial, the combination of riociguat with PDE-5 inhibitors is not recommended. The side effect profile of riociguat is similar to PDE5-i and include dizziness, hypotension, and gastrointestinal symptoms.

Prostacyclin Analogues

Prostacyclin analogues, including epoprostenol, treprostinil, and iloprost, target the prostacyclin pathway, which is significantly impaired in PAH patients, and induce potent vasodilatory and antiproliferative effects. Epoprostenol, the first PAH-approved therapy, remains a cornerstone in the treatment of PAH patients with severe disease but has a short-life, thus requiring a continuous intravenous infusion through a permanent tunnelled catheter. Treprostinil, available in intravenous, subcutaneous, inhaled, and oral forms, provides greater flexibility and is often preferred due to its longer half-life. Iloprost, delivered via nebulization, ensures selective pulmonary vasodilation but requires frequent dosing, which may affect patient compliance.

Subcutaneous or intravenous administration may be associated with adverse reactions, such as infusion site pain or catheter-related bloodstream infections, which may limit patients' tolerability and quality of life. To overcome the significant burden associated with external pump delivery systems, the fully implantable pump system for treprostinil administration has been developed.

Selexipag

Selexipag is an oral prostacyclin receptor agonist, chemically distinct from prostacyclin, which has been shown to reduce the relative risk of composite morbidity/mortality events by 40% in the event-driven phase 3 GRIPHON trial. The most common side effects associated with its administration are headache, diarrhea, nausea and jaw pain.

Sotatercept

Sotatercept, previously tested in hematological diseases, is a novel therapeutic option available for PAH patients administered by subcutaneous injection every 21 days. It acts a class activin signaling inhibitor: sequestering ligands of the transforming growth factor-β superfamily, the drug re-balances the pro- and anti-proliferative signals, inhibits cellular proliferation and promots pulmonary vascular cells apoptosis. In the phase 2 PULSAR and phase 3 STELLAR RCTs, sotatercept showed to improve PVR and exercise capacity. Side effects include epixastis, telangiectasia, thrombocytopenia and increased hemoglobin levels.

Future studies and real-world experience will help PH specialists better define the long-term safety of sotatercept and delineate the patient phenotype to be candidate for this treatment.

Treatment Algorithm and Combination Therapy

Risk stratification using the three strata model at baseline and the four strata model at follow-up guides clinicians in the choice of the best therapeutic strategies. As suggested by ESC/ERS guidelines and the last

World Symposium on pulmonary Hypertension (WSPH), the treatment approach is tailored to individual patient risk profiles:

- ***Vasoreactive patients***: High-dose calcium channel blockers are recommended for patients who demonstrate a significant acute vasodilatory response during the first right heart catheterization.
- ***Not high-risk patients***: an initial dual therapy with an ERA and a PDE-5i is recommended, based on strong evidence supporting the benefits of early combination therapy.
- ***High-risk patients***: a combination therapy including parenteral prostanoids is recommended, as these patients exhibit a poorer prognosis.

An early multiparametric assessment after 3-4 months is essential to identify PAH patients who have not reached or maintained a low-risk status with ongoing therapy.

Patients at intermediate-low risk despite the combination oral therapy should be considered for: adding an oral prostacyclin pathway agent (e.g. selexipag), switching from PDE5-i to riociguat or as recently suggested by the 7th WSPH, adding sotatercept.

Patients at intermediate-high risk or high-risk at follow-up should receive a parenteral prostacyclin pathway agent or be considered for add-on sotatercept. These patients should also be evaluated for lung transplantation.

In the management of PAH patients with comorbidities, great caution should be exercised in choosing the therapeutic approach and a close follow-up should be performed.

Conclusion

Despite significant therapeutic advancements, PAH remains an incurable disease. Optimal treatment involves personalized risk assessment, early combination therapy, and close clinical monitoring. Further research with the discovery of new therapeutic agents and strategies will be crucial in advancing PAH treatment algorithms and improving patient outcomes. Based on the RCTs results, the recent approval of sotatercept will bring great changes in the management of PAH patients. However, we have to wait for its use in real-world life to know further details and to answer many questions.

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