Diagnostic and Therapeutic Advances in Pulmonary Arterial Hypertension Management - A Literature Review

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1. Introduction

Pulmonary Arterial Hypertension (PAH) is a critical health issue characterized by elevated blood pressure within the arteries of the lungs, which can result in heart failure and even mortality. The intricate nature of PAH's onset, its diverse manifestations, and the complexity of its treatment call for a deeper comprehension and sophisticated approaches to management. Progress in research has brought forth new diagnostic methods, treatments, and care approaches, enhancing early detection, prognosis, and patient outcomes. The review underscores the emergence of novel drugs, the evolution of care models, and a deeper grasp of PAH's pathogenesis. It emphasizes personalized care's role in improving life quality for PAH patients and points to future therapy and coordination advancements to better patient prognosis (1). The article serves to update healthcare professionals on PAH management and encourages continued innovation and collaboration to overcome PAH's challenges.

Emerging Insights into Disease Mechanism:
Emerging insights into the disease mechanism of pulmonary arterial hypertension (PAH) have significantly advanced our understanding of this complex condition. Contemporary studies have illuminated the molecular, cellular, and systemic factors that contribute to Pulmonary Arterial Hypertension (PAH), paving the way for the development of innovative treatment options. Key developments include:

- **Precision Medicine**: The move towards precision medicine in PAH involves tailoring treatment to individual patient profiles based on genetic, biomarker, and phenotypic data.(2)
- **Cell Signaling**: Disruptions in cell signaling pathways are central to PAH pathophysiology, with clinical studies exploring new drug targets that address these perturbations. A diminished BMPR2 signaling pathway can lead to inappropriate expression of growth factors and proinflammatory responses (3).
- **Vascular Repair**: The investigation into progenitor cells' contribution to vascular healing and the right ventricle's adaptation to heightened pressure is ongoing. These studies have significant implications for patient outcomes and the development of therapeutic approaches.(2,3)

Novel Biomarkers for Early Detection:
Recent studies have pinpointed new biomarkers with potential for early PAH detection, which could lead to better disease management. A meta-analysis identified markers like red cell distribution width and NT-proBNP, the latter being highly sensitive for PAH. Machine learning has further isolated a protein panel from the DETECT cohort, showing good diagnostic accuracy in distinguishing PAH from non-PH in systemic sclerosis patients. These findings could enhance PAH screening and diagnosis, allowing for more timely treatment (4)

Radiological Advances in Diagnosis of PAH:
Some key advances in radiological techniques and their roles in PAH management include:

- **High-Resolution Computed Tomography:** HRCT Especially beneficial for the assessment of lung parenchyma and identification of underlying diseases that could be contributing to PAH, such as interstitial lung disease. (5)
- **CT Pulmonary Angiography:** CTPA has improved significantly, allowing for better visualization of the pulmonary vasculature and the detection of vascular changes associated with PAH, alongside screening for pulmonary embolism (6).
- **Magnetic Resonance Imaging:** Cardiac MRI has advanced to provide comprehensive non-invasive evaluation of right heart morphology, function, and flow dynamics without ionizing radiation exposure. Enhanced imaging protocols and contrast agents improve the assessment of myocardial fibrosis and perfusion (5).
- **Dual-Energy CT:** DECT allows for the differentiation of materials based on their energy-dependent attenuation characteristics. It's under investigation for more specific pulmonary blood volume assessments and may improve the detection of vascular abnormalities in PAH (7).
- **Ventilation-Perfusion (V/Q) Scan:** While being a classic imaging methodology, V/Q scans remain a critical tool to assess for chronic thromboembolic pulmonary hypertension, which requires different therapeutic approaches than other types of PAH.
- **Echocardiography:** Improvements in echocardiography technology have enhanced the ability to estimate pulmonary artery pressures and assess right heart function with greater accuracy also estimates the cardiac response to raised pulmonary vascular pressure (7).
- **Positron Emission Tomography:** PET, often combined with CT (PET/CT), allows for metabolic imaging which can help in research applications to understand the molecular pathways involved in PAH (7).
- **Intravascular Ultrasound:** IVUS may be used during procedures such as a pulmonary balloon angioplasty for CTEPH to assess the pulmonary arteries more accurately than traditional angiography.

Advances in Pharmacoltherapy:

- **Sotatercept (winrevair)**: The Food and Drug Administration (FDA) has recently given the green light this novel medication for adult patients who are affected

with pulmonary arterial hypertension. As an injectable form of therapy, Winrevair introduces a new category of treatment by inhibiting activin signaling. The endorsement of Winrevair came on the heels of the Phase III STELLAR trial outcomes, which revealed that the addition of Winrevair to the existing standard care led to a notable 41-meter increase in the six-minute walk test over 24 weeks and a substantial 84% decrease in the risk of mortality and PAH-related health deterioration events(8).

- **New Single-Tablet Combination of Macitentan and Tadalafil:** Approved on March 27, 2024 by FDA, this combination therapy is designed to address the underlying vascular cell proliferation in PAH(9). The rationale for combining macitentan and tadalafil for the treatment of pulmonary arterial hypertension (PAH) is based on their complementary mechanisms of action targeting different pathways involved in the disease. Macitentan is an endothelin receptor antagonist (ERA) that blocks the effects of endothelin-1, a potent vasoconstrictor, thereby reducing pulmonary vascular resistance and preventing vascular remodeling. Tadalafil is a phosphodiesterase type 5 inhibitor (PDE5i) that enhances the effects of nitric oxide, leading to vasodilation in the pulmonary vasculature. Clinical studies have shown that the initial combination therapy with an ERA and a PDE5i, such as macitentan and tadalafil, can improve cardiopulmonary hemodynamics, functional capacity, and long-term outcomes in newly diagnosed PAH patients compared to monotherapy. The single-tablet combination of macitentan and tadalafil simplifies the treatment regimen, potentially improving adherence and patient outcomes (10).
- **Uptravi (selexipag)**: This medication is an oral agent that activates prostacyclin receptors. Its mechanism involves expanding the lung's blood vessels, thereby reducing pulmonary pressure. This action has the potential to slow the advancement of the disease and lessen the likelihood of hospital admissions due to PAH. The FDA, in 2021, sanctioned an intravenous version of Uptravi for adults with PAH who are momentarily unable to undergo oral treatment. This decision was informed by a Phase 3 clinical trial that evaluated the safety and pharmacological properties of alternating between oral Uptravi and its IV counterpart. The availability of the IV form ensures continuous treatment, which is vital due to the progressive nature of PAH (11)
- **Tyvaso DPI (Treprostinil)**: Approved by FDA in 2022 for the treatment of pulmonary arterial hypertension (PAH). Tyvaso DP is an inhalation powder form of Treprostinil, a prostacyclin analog that helps to dilate blood vessels in the lungs and reduce blood pressure and this was supported by the BREEZE study(12).The research indicated that for individuals suffering from pulmonary hypertension as a consequence of interstitial lung disease, the administration of inhaled Treprostinil led to enhanced physical endurance. This was evidenced by a notable increase in the 6-minute walk distance over a 16-week treatment duration. Moreover, inhaled Treprostinil was linked to a diminished likelihood of clinical deterioration compared to a placebo, a decrease in NT-proBNP concentrations, and a reduction in the frequency of exacerbations related to the primary lung condition (13).
- **ILOPROST: Iloprost** a prostacyclin analogue recently approved by FDA as inhalational drug therapy for PAH. They work by dilating the blood vessels in the lungs, which reduces the pressure in these vessels and helps to improve symptoms and exercise capacity in patients with PAH. Iloprost is available as an inhalation solution and is typically administered 6 to 9 times daily, which can be burdensome for patients due to the frequent dosing schedule
- **Treprostinil:** It is also a prostacyclin analogue recently approved by FDA. It comes in various forms, including oral, inhalation, subcutaneous, and intravenous. The inhaled form of Treprostinil is usually administered 4 times a day, which may be more convenient compared to iloprost(1)A recent study compared the adherence, persistence, and healthcare resource utilization between patients with PAH who initiated treatment with inhaled Treprostinil versus iloprost. The study found that adherence and persistence were significantly better with inhaled Treprostinil, and it was associated with fewer hospitalizations and emergency department visitv (4).
- **Yutrepia** (active ingredient: Treprostinil, developed by Liquidia Technologies) is a medication that acts as a prostacyclin agonist. It is designed to enhance the exercise capacity of adults diagnosed with New York Heart Association functional class II-III symptoms. The FDA has scheduled its review for March 31, 2024.
- **Opsynvi** (a combination of macitentan and tadalafil, produced by Actelion/Johnson & Johnson) serves as an ERA/PDE5 inhibitor. It is intended for the management of PAH in adults who are classified under WHO functional class II–III. The FDA's review of this medication is expected to take place on March 30**,** 2024 (15)

Interventional and Surgical Procedures

The latest interventional and surgical procedures for pulmonary arterial hypertension (PAH) include a variety of techniques aimed at managing the condition, especially in cases where medical therapy is insufficient. Here are some of the key advancements (16):

- **Atrial Septostomy**: This procedure creates a communication between the right and left atria, allowing for decompression of the right atrium and improved cardiac output.
- **The Potts Shunt:** It is a surgical procedure that creates a channel between the left pulmonary artery and the descending aorta, aiming to alleviate pressure in the right ventricle.
- **Pulmonary Thromboendarterectomy (PTE)**: A surgical cure for chronic thromboembolic PAH (CTEPH), which involves removing organized clotted blood from the pulmonary arteries.
- **Lung Transplantation**: For patients with advanced PAH, lung transplantation remains the definitive treatment option.
- **Veno-Arterial Extracorporeal Membrane Oxygenation (V-A ECMO)** is employed as a temporary therapeutic measure for individuals with advanced PAH, especially in the context of lung transplants and for post-surgical conditioning of the left ventricle.

- **Pulmonary Artery Denervation (PADN)**: A newer interventional technique that may improve transplant-free survival in PAH patients by denervating the pulmonary artery to reduce sympathetic overactivity(16).

These procedures are part of an interdisciplinary approach to PAH treatment, combining pharmacological, interventional, and surgical modalities to improve patient outcomes. For more detailed information, you can refer to the full articles and reviews linked in the references.

Potential of Gene Therapy and Personalized Medicine
Gene therapy holds promise in PAH treatment, targeting defective genes and malfunctioned gene expression involved in the disease. Personalized medicine is another exciting frontier, with the potential to tailor treatments based on a patient's unique genetic profile, environmental factors, and lifestyle choices. This approach could enhance the efficacy of therapy, reduce adverse effects, and proactively prevent the onset of illnesses.

Epigenetic factors are also gaining attention, as they play a significant role in PAH by regulating chromatin structure and altering the expression of critical genes. The integration of multi-omics could help understand the molecular signature of PAH patients, leading to personalized treatment approaches(17).

Lifestyle modifications and supportive care: It plays a crucial role in the management of pulmonary arterial hypertension (PAH). These non-pharmacological strategies can significantly improve the quality of life and potentially enhance the effectiveness of medical treatments. Here are some key aspects:

- **Exercise**: Regular physical activity tailored to individual capabilities can help improve cardiovascular fitness and endurance.
- **Diet**: A balanced diet with attention to nutritional needs is important. Sodium restriction may be advised to manage fluid retention.
- **Psychological Support**: Dealing with a chronic illness like PAH can be stressful. Psychological support and counseling can help patients cope with the emotional aspects of the disease.
- **Oxygen Therapy**: Some patients may require supplemental oxygen to maintain adequate oxygen levels in the blood.
- **Smoking Cessation**: It's critical for patients with PAH to avoid smoking, as it can exacerbate the condition.
- **Avoidance of Certain Medications**: Some over-the-counter medications and prescription drugs can worsen PAH and should be avoided.
- **Pregnancy Management**: Pregnancy can pose significant risks in PAH, and family planning should be discussed with healthcare providers

2. Conclusion

Pulmonary hypertension poses a great challenge in the current era in terms of early detection, management and dreaded complication for delayed detection or treatment. Multidisciplinary approach is necessary to manage PAH. More research is required to apply the advanced principles in management.

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