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Review Article
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# Future Perspectives of Pulmonary Hypertension Treatment

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Since the discovery of three major pathophysiological mechanisms of pulmonary arterial hypertension (PAH), including prostacyclin, endothelin and nitric oxide pathways, the therapeutic options for PAH have increased. Nevertheless, despite these advances, the prognosis remains unsatisfactory for many patients with PAH. With the progress of both pre-clinical and clinical research on PAH, several novel therapeutic targets have been identified for the treatment of PAH. In this study, we review updated information of novel pathophysiological pathways of pulmonary hypertension, mainly focusing on WHO Group I PAH. Drugs based on these pathways are currently under clinical or pre-clinical investigation, however they have been approved for clinical use. Large clinical trials are required to validate the clinical safety and effects of these novel therapies.

**Key Words:** Clinical trial • Novel therapy • Pre-clinical study • Pulmonary arterial hypertension

## INTRODUCTION

Since the discovery of three pathways involved in the pathogenesis of pulmonary arterial hypertension (PAH), namely prostacyclin, endothelin, and nitric oxide (NO) pathways, advances in medical therapies have not only improved functional capacity but also the survival of patients with PAH.[1] Nevertheless, there remain unmet needs with regards to treating these patients. With the discovery of novel mechanisms of PAH, targets including immune and inflammation regulation, genetic therapy, modification of mitochondrial dysfunction, tyrosine kinase inhibitors, stem cell therapy, and pulmonary artery denervation therapy (PADN) suggest the potential development of new drugs.[2] In this review, we briefly summarize updated information on novel medications and ongoing clinical trials (Figure 1).

## SYSTEMIC HYPERTENSION VS. PULMONARY HYPERTENSION

Despite evidence of the therapeutic effects of β-

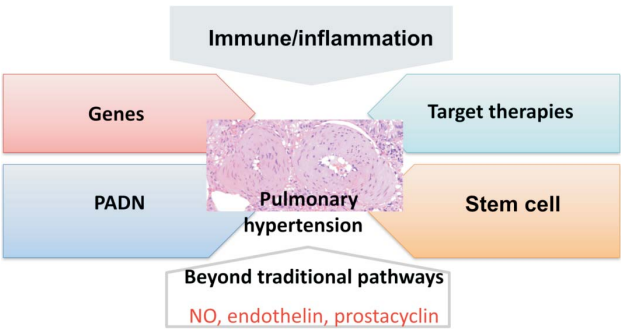


***Figure 1.*** *Illustration of novel therapies for pulmonary hypertension. NO, nitric oxide; PADN, pulmonary artery denervation.*

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blockers, angiotensin-converting enzyme inhibitors (ACEis)/angiotensin receptor blockers and aldosterone antagonists in patients with left heart failure, their effects on pulmonary hypertension are still under debate.[3] Notably, though ACEis have an important renoprotective effect in patients with scleroderma, they have not been shown to be beneficial in patients with PAH.[2,4] Likewise, a randomized study testing bisoprolol in patients with idiopathic PAH showed decreases in cardiac index and exercise capacity.[5] The single-center, double-blind, randomized controlled PAHTCH study focused on the effect of carvedilol on pulmonary hypertension-related heart failure. The results showed that carvedilol did not significantly improve N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels or 6-minute walk distance (6MWD) after 24 weeks of treatment, however larger studies are necessary to verify the long-term benefits of the use of β-blockers in pulmonary hypertension.[6] In addition, prospective studies examining the therapeutic effect of the aldosterone antagonist, spironolactone, are currently underway.[7]

## IMMUNE/INFLAMMATORY

Recent studies have revealed that immune and inflammatory responses play crucial roles in the pathogenesis of idiopathic and connective tissue disease-associated PAH.[8] Ubenimex, an inhibitor of the inflammatory mediator leukotriene B4, failed to achieve the primary end-point in the LIBERTY trial. In patients with Group I PAH, ubenimex did not significantly improve pulmonary vascular resistance (PVR) or increased the 6MWD, which was the secondary goal of the study (Table 1). Rituximab, a monoclonal antibody targeting CD20+ B-cells, showed acceptable drug safety. Although in the primary analysis at week 24, the change in 6MWD showed an insignificant improvement, B-cell depletion therapy could be a potentially safe and effective adjuvant treatment for patients with systemic sclerosis-related PAH.[9] From another perspective, cytokines such as interleukins (ILs) have been linked to the pathogenesis of PAH through their ability to regulate cell migration, differentiation and proliferation.[10] Nevertheless, tocilizumab, a monoclonal antibody to the IL-6 receptor, failed to show improvement in PVR, the primary end-point, in patients with WHO Group 1 PAH in an open-label phase 2 trial.[11] Despite a reduction in C-reactive protein and an increase in IL-6, tocilizumab did not improve functional status, 6MWD or NT-proBNP. Elafin, an endogenously produced elastase inhibitor, has now progressed to clinical trials.

## MITOCHONDRIAL DYSFUNCTION

Mitochondrial dysfunction may induce PAH development through vascular remodeling.[12] In diseased pulmonary vessels and right ventricle, a shift from mitochondrial oxidation to glycolysis has also been observed.[13] Bardoxolone methyl, an Nrf2 activator and inhibitor of the NF-κB pathway, showed positive results in 6MWD in a phase 2 study (LARIAT; NCT02036970) on background therapy (Table 1).[14] However, two subsequent clinical trials, the RANGER and CATALYST studies, were terminated due to the COVID-19 pandemic.

## GENETIC TARGETS

Genetic studies on familial PAH have revealed heterozygous germline mutations in the bone morphogenetic protein 2 receptor (BMPR2), a receptor for the transforming growth factor (TGF)-β/BMP family.[15,16] Notably, about one fifth of patients with sporadic idiopathic PAH have been reported to have decreased expressions of BMPR2.[17] Thus, the critical role of the BMPR2 pathway in the pathogenesis of PAH implies a treatment option for PAH. Tacrolimus (FK506), an activator of BMPR2-mediated signaling, and ataluren, a read-through of missense mutations, have both been shown to increase BMP expression (Table 1).[18,19] Alternatively, sotatercept, a novel activin-receptor fusion protein which increases BMP signaling through inhibiting TGF-β activity, was found to reduce pulmonary vascular resistance in PAH patients receiving background therapy in the PULSAR Trial.[20] Sotatercept was also associated with a decrease in NT-proBNP levels. Nevertheless, hematologic adverse events including thrombocytopenia and increased hemoglobin levels should be evaluated during treatment.

**Table 1.** The summary of novel drugs, experimental and clinical studies in pulmonary hypertension

| Novel therapies | Drugs | Rationales | Clinical trials | Study design | Main inclusion criteria | Study duration | Main outcomes | Current status |
|---|---|---|---|---|---|---|---|---|
| Immune and inflammation | Ubenimex | An oral, small-molecule inhibitor of leukotriene $A_4$ hydrolase ($LTA_4H$), associated with the inflammation | LIBERTY study (NCT02664558) | A multicenter, randomized, double-blind, placebo-controlled phase 2 study | WHO Group 1 PAH | 24 weeks | Changes in PVR | Completed. not yet published |
| | | | LIBERTY II (NCT02736149) | An open-label extension phase 2 study | WHO Group 1 PAH | 24 weeks | Safety | Terminated (failed to demonstrate effectiveness) |
| | Rituximab | A monoclonal antibody which can target the CD20+ B-cells in plexiform lesions in PAH | NCT01086540 | A multicenter, randomized, double-blind, placebo-controlled phase 2 study | SSc-PAH | 2 intravenous infusions, follow 24 weeks | 6MWD | Completed and published[9] |
| | Tocilizumab | A monoclonal antibody to the IL-6 receptor to control cell migration, differentiation and proliferation | TRANSFORM-UK (NCT02676947) | An open-label phase II trial | Group 1 PAH | 6 months | Primary: Safety and PVR; Secondary: 6MWD | Completed and published (no significant improvement)[11] |
| | Elafin | An endogenously produced elastase inhibitor | NCT03522935 | A phase I study (safety of subcutaneous Elafin) | Healthy Subjects | 4 weeks | Safety | Completed, not published |
| Mitochondrial dysfunction | Bardoxolone methyl | A Nrf2 (a protein that protects against oxidative damage) activator and inhibitor of the NF-κB pathway | LARIAT; NCT02036970 | A phase II study (Part 1: RCT, Part 2: open labeled) | WHO Group I, III, or V PH | 16 weeks | 6MWD | Completed and published (positive results in 6MWD)[14] |
| | | | RANGER (NCT03068130) | A phase III trial | Healthy Subjects | 6 years | Long term safety | Terminated (due to COVID-19) |
| | | | (CATALYST; NCT02657356) | A randomized, double-blind, placebo-controlled phase II | CTD related PAH | 24 weeks | 6MWD | Terminated (due to COVID-19) |
| Bone morphogenetic protein receptor type 2 (BMPR2) signaling | Tacrolimus (FK506) | A calcineurin inhibitor activates BMPR2 | TransformPAH (NCT01647945) | Single-center randomized controlled phase II study | WHO Group I PAH | 16 weeks | Safety and efficacy of FK-506 (Tacrolimus) | Low-level FK506 is well tolerated and increases BMPR2 in subsets of PH patients[10] |
| | Sotatercept (ACE-011) | Increase BMP and inhibit TGF-β activity. A novel activin-receptor fusion protein | PULSAR (NCT03496207) | Phase 2, double blind, randomized, placebo-controlled | WHO Group I PAH, functional class II~III | 24 weeks | Primary: PVR; Secondary: 6MWD, NT-proBNP, echo parameters, CAMPHOR | Complete (reduction of PVR and NT-proBNP)[20] |
| | | | SPECTRA (NCT03738150) | This is a phase 2a, single arm, open-label | In adults with WHO functional class III pulmonary arterial hypertension (PAH). | 24 weeks | The effects of sotatercept on peak oxygen uptake (VO2 max) and RV function | Active, not recruiting |
| | | | STELLAR (NCT04576988) | Phase 3, randomized, double-blind, placebo-controlled | WHO Group I PAH | 24 weeks | 6MWD, NT-proBNP, functional class | Recruiting |

**Table 1.** Continued

| Novel therapies | Drugs | Rationales | Clinical trials | Study design | Main inclusion criteria | Study duration | Main outcomes | Current status |
|---|---|---|---|---|---|---|---|---|
| DNA damage | Olaparib | An orally available PARP1 inhibitor approved for the treatment of BRCA related breast cancer | OPTION multicenter (NCT03782818) | Early phase 1, 2 | PAH of idiopathic/ hereditary/drug or toxin-induced origin or CTD (Fc II or III) | 24 weeks | Primary: treatment-emergent AEs at week 24; Secondary: 6MWD, functional class | Recruiting |
| Tyrosine kinase inhibitors (TKIs) | Nilotinib (AMN107) | A TKI approved in CML | NCT01179737 | A phase II trial of nilotinib in patients with PH | PAH, Fc II or III | 168 days | Primary: Change in PVR Secondary: 6MWD, SAE | Terminated due to serious adverse events[30] |
| | Imatinib (STI-571) | A TKI, proven for CML and $Ph^+$ ALL and GIST | IMPRES: Imatinib (QTI571) in Pulmonary Arterial Hypertension (NCT00902174) | Phase 3 | WHO Group I PAH, Fc II~IV | 24 weeks | in 6MWD and in hemodynamic parameters | Published (significant improvements but was terminated due to subdural hematoma)[31] |
| | | | PIPAH: Positioning Imatinib for Pulmonary Arterial Hypertension (NCT04416750) | Phase 2 | WHO Group I PAH | 24 weeks | The highest tolerated dose, PVR | Recruiting |
| Stem cells | Endothelial progenitor cells (EPCs) | Capability in regeneration of endothelial lining of blood vessels | PHACeT: eNOS transfected EPCs (NCT00469027) | Phase 1 | IPAH | 12 weeks | Primary: tolerability and safety; Secondary: potential efficiency | Completed (well tolerated with short-term hemodynamic improvement)[38] |
| | | | eNOS-enhanced EPCs SAPPHIRE (NCT03001414) | Phase 2/3 | IPAH | 6 months | 6MWD | Recruiting |
| | | | In an infusion of autologous EPCs (NCT00641836) | Phase 2/3 | WHO Group I PAH | 12-week | 6MWD | Completed (Improvement in 6MWD and hemodynamic parameters)[37] |
| | Cardiosphere-derived cells (CDCs) | Cardiac progenitor cells with regenerative properties | ALPHA (NCT03145298) | Phase 1 | IPAH, HPAH, PAH-CTD, PAH-HIV | 2 weeks | Primary: Gas exchange and hemodynamics; secondary: safety | Recruiting |

**Table 1.** Continued

| Novel therapies | Drugs | Rationales | Clinical trials | Study design | Main inclusion criteria | Study duration | Main outcomes | Current status |
|---|---|---|---|---|---|---|---|---|
| Pulmonary artery denervation (PADN) | PADN | Ablating the nerves regulating sympathetic tone in the pulmonary artery | chiCTR-ONC-12002085 | Phase 2 | PH (heterogenous etiologies) | 6 months | Primary: 6MWD; Secondary: hemodynamic parameters | Complete (improvements in 6MWD and hemodynamic parameters)[42] |
| | | | TROPHY-I (NCT04570228) | Phase 1 | WHO Group I PAH | 12 months | Primary: safety; Secondary: 6MWD | Complete (improvements in 6MWD and PVR)[43] |
| | | | PADN-5 (NCT02220335) | Phase 1 | Combined pre- and post-capillary PH associated left heart failure | 6 months | Primary: safety, PVR; Secondary: 6MWD | Complete (improvements in PVR and 6MWD)[41] |
| | | | TROPHY-II (NCT03611270) | Phase 1 | WHO Group II PH | 4 months | Primary: safety; Secondary: 6MWD | Recruiting |

BMPR2, bone morphogenetic protein receptor type 2; CAMPHOR, Cambridge Pulmonary Hypertension Outcome Review; CDCs, cardiosphere-derived cells; CTD, connective tissue disease; EPCs, endothelial progenitor cells; IL, interleukin; PADN, pulmonary artery denervation; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; SSc, systemic sclerosis; TKIs, tyrosine kinase inhibitors; 6MWD, 6-minute walk distance.

## EPIGENETIC MODIFICATION AND DNA DAMAGE

Epigenetic modification indicates changes in phenotype by altering the post-transcriptional gene expression.[21] Epigenetic-sensitive alterations can deregulate interactome flow leading to vascular remodeling in PAH.[21,22] In pre-clinical cell and animal models of PAH, histone deacetylase has shown beneficial effects, however its potential cardiotoxicity is a concern.[23,24] Also, high levels of DNA damage were observed in the lungs and arterial tissues in patients and animal models of pulmonary hypertension.[25] Through binding to DNA strand breaks, poly(ADP-ribose) polymerase-1 (PARP1) generates large amounts of poly(ADP-ribose) along the break site, thereby triggering DNA repair and promoting cell survival. Also, by producing high levels of IL-6, PARP-1 activates the STAT3/NFAT/HIF-1$\alpha$ pathway which promotes apoptosis resistance in pulmonary smooth muscle cells.[26] PARP1 activates proliferation despite the presence of DNA-damaging insults, eventually leading to PAH.[25] In several animal models, the suppression of PARP could reverse the development of PAH.[25,27] In an open-label phase 1 study, olaparib, an orally available PARP1 inhibitor which has been approved for the treatment of BRCA (breast cancer gene)-associated breast cancer, has been proposed for PAH patients (Table 1).[17,19]

## TYROSINE KINASE INHIBITORS (TKIs)

The relationship between TKIs and PAH is currently indeterminate.[28] Nilotinib, which has been approved for chronic myelogenous leukemia, was shown to prevent angioproliferation in a rodent model of systemic sclerosis-induced pulmonary hypertension.[29] However, a phase 2 trial of nilotinib in patients with PAH was terminated due to serious adverse events (Table 1).[30] Another TKI, imatinib, was investigated in a phase 3 trial (IMPRES).[31] Despite significant improvements in 6MWD as well as in hemodynamic parameters, imatinib treatment was associated with high incidence rates of drug discontinuation and subdural hematoma.[31] To avoid the systemic toxicities of TKIs, inhaled forms have been developed. Another phase 1 study focusing on the safety, tolerability and pharmacokinetics of inhaled imatinib (AER-901) is ongoing (NCT04903730). Also, GB002, a small molecule

that targets PDGFR$\alpha/\beta$, CSF1R, and c-KIT, and modulates BMPR2, has been formulated for inhalation delivery to directly target the diseased lung. A phase 2 study has been launched to evaluate its efficacy and safety in adult subjects with Group 1 PAH (NCT04456998). Conversely, exposure to dasatinib has been associated with the development of PAH.[32,33] Similarly, sorafenib, a multikinase/angiogenesis inhibitor, has also shown controversial findings. In a single-center, open-label trial of 12 patients with PAH, sorafenib worsened pulmonary hemodynamics and was associated with adverse events.[34] In contrast, in another study of 9 patients who had severe and refractory PAH, as a combination therapy, sorafenib had favorable effects.[35]

## STEM CELLS

Although stem cell therapies targeting the RV have shown promising results in animal models, the results of a recent multicenter human trial were indeterminate.[36] A few clinical reports have investigated autologous endothelial progenitor cell (EPC) therapy in patients with PAH, and they have shown improvements in 6MWD and hemodynamic variables.[37] For example, using eNOS-transfected EPCs, the PHACeT study showed good tolerance and a short-term hemodynamic improvement.[38] Another type of cardiac stem cell, cardiosphere-derived cells (CDCs), which are potently angiogenic, antifibrotic and antiapoptotic, have also shown benefits in animal models of PAH.[39] A phase 1 trial using allogeneic CDCs for PAH is ongoing. To date, stem cell therapies seem to be a double-edged sword for PAH development, and current evidence is still inconclusive (Table 1).

## PULMONARY ARTERY DENERVATION (PADN)

Elevated plasma norepinephrine and muscle sympathetic nerve activity have been reported in several studies, and the neurohormonal axis is a potential therapeutic target in PAH.[40] The process of PADN involves ablating the nerves regulating sympathetic tone in the pulmonary artery, disrupting the non-vagal pulmonary baroreceptor reflex.[40] In small proof-of-concept studies, PADN showed benefits in targeted medical therapy for patients with combined pre- and post-capillary pulmonary hypertension (CpcPH) secondary to left-sided heart failure.[41] An open-label phase 2 trial showed that PADN improved 6MWD and hemodynamic parameters in patients with PH, defined as a resting mean PAP (mPAP) $\geq$ 25 mmHg, as measured by right heart catheterization (Table 1).[42] Likewise, in another phase 1 study (TROPHY-I) which used intravascular ultrasound guidance, PADN reduced PVR and increased 6MWD at 4 and 6 months follow-up in PAH patients without serious adverse events.[43] Regarding CpcPH, the PADN-5 Study showed that PADN significantly improved 6MWD in patients with CpcPH associated with left heart failure.[41] Meanwhile, another phase 1 study (TROPHY-II) also focusing on the safety of PADN in WHO Group II PAH is ongoing.

## CONCLUSIONS

In this review, we summarized updated information of both experimental and clinical studies on novel therapies for PAH. However, there is still a large gap between the experimental data, which focuses on a rather homogenous animal population, and human clinical data, which is far more heterogeneous with multiple comorbid conditions. Differences in the dose, duration of therapy, and complexities of disease models between human and animals mean that animal model data cannot mimic use of the drug in PAH patients. Nevertheless, these concerns should not cause researchers to abandon testing PAH candidate drugs. In contrast, pre-clinical trials such as phase 1 and 2 trials should play roles in training investigators on how to improve the efficiency of the entire process. Rather than using conventional clinical and hemodynamic end-points such as hemodynamic variables and 6MWD, the end-points should be tailored to different groups and their anticipated mechanisms. Larger clinical trials are still required to validate the clinical safety and effects of these novel therapies. Emerging evidence will enhance the contents of clinical guidelines on PAH.[44]

## CONTRIBUTORS

All authors contributed equally to the searches, de-

sign and writing of the manuscript.

## PATIENT CONSENT FOR PUBLICATION

Not required.

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## DECLARATION OF CONFLICT OF INTEREST

All the authors declare no conflict of interest.

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