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Recent Advances in Targeted Therapy for Connective Tissue Disease-associated Pulmonary Arterial Hypertension

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Abstract: Pulmonary arterial hypertension (PAH) is a common and severe vascular complication in patients with connective tissue diseases (CTDs), and it also represents a leading cause of adverse outcomes and mortality in this population. Over the past decades, the continuous emergence of effective therapeutic approaches targeting the key signaling pathways of PAH has significantly alleviated patients' symptoms and improved their quality of life. As a crucial subtype of PAH, patients with connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH) have also gained substantial benefits from these advances. Targeted therapy serves as the core treatment modality, and in recent years, numerous breakthroughs have been achieved in the field of CTD-PAH targeted therapy. This article systematically reviews the latest research progress of both traditional and emerging targeted therapies for CTD-PAH.

Keywords: Pulmonary Arterial Hypertension; Connective Tissue Disease; Pharmacotherapy; Targeted Therapy.

1. Introduction

Pulmonary hypertension (PH) refers to a category of hemodynamic disorders characterized by elevated intravascular pressure in the pulmonary circulation. According to the latest joint guidelines released by the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) in 2022, CTD-PAH is classified into Group 1 (i.e., the PAH group) of the PH classification system [1]. Its core pathological features include pulmonary vascular remodeling, involving medial hypertrophy of small pulmonary arteries, intimal fibrosis, plexiform lesions, and occlusion of micro-pulmonary arteries. Progressive elevation of pulmonary arterial pressure and vascular resistance eventually leads to right heart failure and death[2, 3] . PAH is the second-largest subtype in the PAH group following idiopathic pulmonary arterial hypertension (IPAH), accounting for approximately 10%–30% of all PAH cases globally [4] and around 13%–14% in the Chinese population[5] . It is a major contributor to mortality and poor prognosis in CTD patients. The pathogenesis of CTD-PAH has not been fully elucidated, but existing studies suggest that it is closely associated with chronic inflammatory responses mediated by immune dysregulation. Inflammation is regarded as the initial trigger, which can induce endothelial cell (EC) dysfunction, abnormal proliferation of smooth muscle cells (SMCs) and fibroblasts, thereby leading to pulmonary vascular remodeling. This process ultimately results in increased pulmonary vascular resistance (PVR) and the onset of PAH[6-8] . At present, targeted therapies for PAH mainly focus on three core signaling pathways, including drugs targeting the nitric oxide (NO) pathway (phosphodiesterase 5 inhibitors, soluble guanylate cyclase stimulators), endothelin receptor antagonists (ERAs), and the prostacyclin pathway (prostacyclin analogues, IP receptor agonists)[9] . Although the application of targeted drugs has significantly improved the prognosis and delayed disease progression in CTD-PAH patients, the high mortality rate and irreversible disease progression still pose severe challenges to clinical treatment[10] .

In recent years, a growing body of research has indicated that CTD-PAH-specific therapies developed based on the genetic and molecular mechanisms underlying small vessel injury and obstructive vascular remodeling may yield better prognostic outcomes and even reverse vascular remodeling[11]. Therefore, this review systematically summarizes the latest research advances in both classic and emerging targeted drugs for CTD-PAH.

2. Conventional Targeted Therapy

2.1. Prostacyclin Analogues

The prostacyclin pathway is one of the core pathways for PAH targeted therapy. Its key therapeutic mechanism for CTD-PAH is to exert synergistic effects such as vasodilation, anti-proliferation, and anti-inflammation by regulating critical signaling molecules[12]. Under physiological conditions, prostacyclin (PGI_2) specifically binds to IP receptors on the surface of pulmonary vascular smooth muscle cells, activates adenylate cyclase (AC), and promotes the conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP). As a second messenger, cAMP inhibits the contraction and abnormal proliferation of pulmonary vascular smooth muscle cells, while suppressing platelet aggregation, thus maintaining the normal vasodilatory function and structural stability of pulmonary vessels[12]. In the pathological state of CTD-PAH, immune-inflammatory damage caused by CTD itself severely impairs pulmonary vascular endothelial function, leading to reduced synthesis and release of PGI_2. This attenuation of protective effects further exacerbates pulmonary vascular remodeling, elevation of pulmonary arterial pressure, and increased right ventricular load. Therefore, exogenous supplementation of PGI_2 analogues or direct activation of IP receptors via targeted drugs acting on the prostacyclin pathway can restore local cAMP levels in pulmonary vessels, reverse abnormal

vasoconstriction and proliferation, exert anti-inflammatory and anti-thrombotic effects, and ultimately reduce pulmonary arterial pressure and PVR, improving cardiac function and long-term prognosis in CTD-PAH patients[13, 14]. For PAH patients with WHO functional class II–IV, prostacyclin analogues or prostacyclin receptor agonists are recommended[15], among which prostacyclin analogues remain the cornerstone of first-line therapy for high-risk PAH patients. Currently, approved prostacyclin pathway-related drugs for PAH treatment include epoprostenol, iloprost, treprostinil, beraprost, and selexipag. Adverse reactions of these drugs are mostly associated with non-selective vasodilation, with headache, facial flushing, jaw pain, and diarrhea being the most common. Parenteral administration of prostacyclin analogues is the main treatment method for PAH, but relevant research on their application and prognosis in CTD-PAH is relatively limited. Recently, a single-center retrospective study in Australia (n=39) showed that CTD-PAH patients accounted for 46.2% of the cohort (predominantly females with WHO functional class III–IV), with a mean duration of epoprostenol treatment of 2.9 years. The 1-year, 3-year, and 5-year survival rates after treatment reached 90.0%, 75.8%, and 68.2%, respectively, which were significantly higher than those of the control group. Meanwhile, the WHO functional class of patients was significantly improved, and the 6-minute walk distance (6MWD) increased by an average of 160.4 meters compared with the baseline at the 3rd year of treatment, indicating that epoprostenol can significantly improve the prognosis of severe CTD-PAH patients[16]. It is worth noting that the incremental benefit may be limited in patients receiving intensive background therapy. A European multicenter retrospective study involving 91 CTD-PAH patients showed that after pretreatment with ≥1 PAH targeted drug (84% receiving dual/triple combination therapy and 16% receiving monotherapy), additional use of parenteral prostacyclins (epoprostenol or treprostinil) could improve functional indicators such as 6MWD and brain natriuretic peptide (BNP) in the short term, but the long-term survival rate remained unsatisfactory (5-year survival rate of approximately 55%), suggesting that the additional benefit of parenteral prostacyclin analogues is limited[17]. In addition to directly improving PAH-related symptoms, prostacyclins can also delay vascular complications of CTD through their anti-inflammatory effects, bringing additional benefits to CTD-PAH patients. A prospective cohort study including 134 systemic sclerosis (SSc) patients demonstrated that long-term use of inhaled iloprost could delay the progression of SSc and significantly postpone the onset of major vascular complications including PAH (such as digital ulcers and scleroderma renal crisis) [18]. However, this study adopted a retrospective design, and the sample size of patients with major vascular complications was small (only 12 cases), so the conclusions need to be further verified by large-scale prospective studies.

Prostacyclin Receptor Agonists

Selexipag is a selective prostacyclin receptor agonist with a chemical structure different from prostacyclin, administered orally. A subgroup analysis of the global multicenter GRIPHON study (n=334) showed that regardless of background targeted therapy, selexipag reduced the risk of the primary composite endpoint of morbidity and mortality by 41% in CTD-PAH patients [19]. A recent real-world study (EXPOSURE study, n=178) further indicated that early initiation of full-dose selexipag in combination with other drugs during the low/medium-risk stage of the disease may lead to better clinical outcomes[20]. Subsequently, a real-world simulated randomized trial by Burger et al. based on the US Komodo insurance database (including CTD-PAH patients, n=718) showed that in PAH patients receiving combined ERA and PDE5i therapy, early addition of oral selexipag within 6 months reduced the risk of all-cause hospitalization, PAH-related hospitalization, and disease progression. This risk reduction was more significant when selexipag was added within 3 months. In contrast, delayed addition of oral selexipag for 12 months or the presence of obvious treatment gaps may result in poor outcomes in PAH patients. These findings suggest that early initiation of treatment after PAH diagnosis in CTD patients can improve long-term prognosis[21]. In addition, a phase II clinical trial of the novel oral prostacyclin receptor agonist ralinepag has confirmed its safety and tolerability, which can continuously improve 6MWD in patients (median improvement of 41.0 meters compared with baseline) and reduce PVR, with manageable adverse reactions compared with other prostacyclin pathway-related drugs[22, 23]. Currently, phase III clinical trials of this drug are underway overseas, which is expected to provide better therapeutic effects and options for CTD-PAH patients in the future.

2.2. Phosphodiesterase 5 Inhibitors and Soluble Guanylate Cyclase Stimulators

Dysfunction of the nitric oxide pathway is a key inducement of pulmonary arterial hypertension. Under normal circumstances, endogenous NO binds to soluble guanylate cyclase (sGC) in pulmonary vascular smooth muscle cells, activating sGC to catalyze the conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). As a second messenger, cGMP relaxes vascular smooth muscle, inhibits pulmonary vascular remodeling, and maintains pulmonary circulatory homeostasis. In the pathological state of PAH, reduced NO production by vascular endothelial cells or decreased sGC activity leads to a decline in cGMP levels, exacerbating pulmonary vasoconstriction and remodeling and increasing PVR[24]. Phosphodiesterase 5 (PDE5) is a key enzyme that degrades cGMP in pulmonary vessels. PDE5 inhibitors enhance the effects of the nitric oxide pathway by slowing down cGMP degradation and increasing endogenous cGMP levels. In contrast, sGC stimulators directly stimulate sGC to promote cGMP production independent of endogenous NO[25].

Phosphodiesterase 5 Inhibitors

In recent years, multiple clinical studies have confirmed that phosphodiesterase 5 inhibitors (PDE5i) can improve various hemodynamic and clinical parameters in CTD-PAH patients [26], and have long been recommended as first-line therapy for CTD-PAH in guidelines at home and abroad. Commonly used PDE5i include sildenafil (short-acting), tadalafil (long-acting), and vardenafil. A growing body of evidence indicates the presence of inflammatory cells and immune cells in the lungs of PAH patients, especially in those with CTD-PAH[27, 28].Clinically, these drugs are mainly used to relax vascular smooth muscle and inhibit pulmonary vascular remodeling in the treatment of CTD-PAH. A recent study by Cassandra et al. suggested that PDE5 inhibitors may have therapeutic potential beyond vasodilation and are expected to be repositioned as adjuvant therapies for

inflammation-driven diseases, especially those characterized by vascular endothelial dysfunction and chronic low-grade inflammation[29]. This dual effect of "vasodilation + anti-inflammation" may be more consistent with the pathological characteristics of PAH secondary to CTD. However, large-scale prospective clinical studies are currently lacking to confirm this hypothesis. In addition, a study by Jin et al. using a CTD-PAH rat model showed that vitamin D deficiency exacerbates pulmonary vascular remodeling and right ventricular hypertrophy in CTD-PAH rats by upregulating the Jagged1/Notch3/Hes1 pathway[30]. Meanwhile, a study by Adao et al. demonstrated that restoring optimal vitamin D (VitD) levels in VitD-deficient rat models can improve pulmonary endothelial function, enhance the vasodilatory response to PDE5i, and improve therapeutic efficacy and exercise capacity[31]. These findings suggest that vitamin D supplementation may serve as an important adjuvant strategy to optimize the efficacy of PDE5i.

Although soluble guanylate cyclase stimulators and PDE5i act on the same pathway, their mechanisms of action are different. sGC stimulators have a dual mechanism: they can both enhance the response of sGC to endogenous NO and directly activate sGC independent of NO. Currently, the main guanylate cyclase stimulator recommended for CTD-PAH treatment is riociguat, which may be an alternative option for CTD-PAH patients with poor response to PDE5i therapy. The REPLACE study randomly assigned PAH patients to the riociguat group (n=113) and the PDE5i group (n=113), with CTD-PAH accounting for 22% and 17% of each group, respectively. The results showed that for medium-risk PAH patients with WHO functional class III and 6MWD of 165–440 m after PDE5i treatment, switching from PDE5i to riociguat significantly increased the 24-week clinical improvement rate compared with continued PDE5i treatment (41% vs 20%), reduced the risk of clinical worsening (1% vs 9%), and decreased hospitalization and mortality events[32]. The limitation is that the sample size of CTD-PAH patients included in this study was small, and the specificity of the conclusions needs further verification. Currently, guanylate cyclase stimulators are mainly administered orally, which may cause systemic side effects, thereby limiting their use or dose escalation and leading to reduced therapeutic efficacy or poor medication compliance. Recently, Humbert et al. [33] evaluated the efficacy and safety of inhaled soluble guanylate cyclase stimulator (MK-5475) in the INSIGNIA-PAH study (n=168), with CTD-PAH accounting for 18.5% of the cohort. The results showed that in PAH patients receiving stable background therapy (including PDE5i), inhaled MK-5475 reduced PVR with good tolerance and no systemic side effects such as hypotension, exhibiting lung-selective pharmacodynamic effects. This finding re-examines the traditional view of contraindicating combined use with PDE5i [34], providing a new option for CTD-PAH treatment, especially suitable for patients requiring intensive combination therapy (e.g., adding drugs on the basis of PDE5i) but concerned about systemic side effects.

2.3. Endothelin Receptor Antagonists

Endothelin-1 (ET-1) binds to endothelin A receptors (ETA) and endothelin B receptors (ETB) on pulmonary arterial smooth muscle cells, promoting vasoconstriction and cell proliferation. ETB receptors are mainly expressed on pulmonary vascular endothelial cells; their activation mediates vasodilation by promoting the production of prostacyclin and nitric oxide, while accelerating the clearance of ET-1 to maintain pulmonary vascular homeostasis[35]. Currently, endothelin receptor antagonists used clinically for CTD-PAH treatment mainly include selective ETA receptor antagonist ambrisentan, as well as dual ETA/ETB receptor antagonists bosentan and macitentan. A subgroup analysis of the previous ARIES-E clinical trial evaluated the efficacy and safety of ambrisentan in CTD-PAH[36]. Subsequently, a study by Li et al. involving 71 Chinese CTD-PAH patients showed that during 24 weeks of treatment, ambrisentan significantly improved exercise capacity in most patients without clinical worsening events, and the adverse events observed in the CTD-PAH subgroup were consistent with the known safety profile of ambrisentan in the overall Chinese PAH population[37]. However, some studies suggest that the efficacy of endothelin receptor antagonists in the treatment of CTD-PAH may be inferior to that in other types of PAH, with more severe adverse reactions. A meta-analysis by Kuang et al. including 659 PAH patients treated with bosentan (CTD-PAH accounting for 8%) showed that the improvement in 6MWD was not statistically significant (p=0.656), only 27.5% of patients had improved WHO functional class, and subgroup analysis indicated that the incidence of hepatotoxicity in CTD-PAH patients was approximately 2 to 4 times higher than that in other groups[38]. This high risk of hepatotoxicity is not only related to endothelin receptor antagonists themselves and combined use with other targeted drugs[39], but also may be associated with the high prevalence of autoimmune hepatitis in CTD, as well as liver function damage caused by CTD itself and CTD treatment drugs [40]. These findings suggest that liver function assessment should be completed and regular monitoring should be performed before making decisions on endothelin receptor antagonist therapy for CTD-PAH patients. Macitentan is an oral dual endothelin receptor antagonist. In the SERAPHIN study, Pulido et al. observed that the drug improved exercise tolerance and reduced the incidence of the composite endpoint of clinical worsening in PAH patients. Subgroup analysis of CTD-PAH patients (n=224) showed that patients were likely to obtain clinical benefits from this drug treatment[41]. Compared with the placebo group, macitentan reduced the risk of morbidity and mortality by 45% in all patients. Subsequently, Souza et al. further evaluated the long-term safety, tolerability, and survival rate of macitentan in PAH patients in its open-label extension study (SERAPHIN OL, n=550) with a follow-up period of up to 9 years, providing important long-term therapeutic evidence for clinical practice [42]. This study included 550 patients, with CTD-PAH accounting for 31.8%, which has important clinical reference value for the long-term treatment of CTD-PAH. Recently, an analysis by Channick et al. [43] based on the combined OPUS/OrPHeUS dataset involving 1192 American CTD-PAH patients showed that macitentan is widely used in the clinical treatment of CTD-PAH and its subgroups (including combination therapy), and its safety and tolerability in CTD-PAH patients are comparable to those in idiopathic/heritable pulmonary arterial hypertension (I/HPAH) patients, providing important evidence for the individualized treatment of CTD-PAH.

3. Emerging Targeted Drugs

Dysregulation of the bone morphogenetic protein (BMP)/transforming growth factor-β (TGF-β) signaling pathway is a core mechanism underlying the development of

PAH, mainly manifested as imbalanced branch signaling. In PAH patients, BMP signaling function is impaired, leading to significantly decreased expression of Smad1/5/8 proteins that mediate anti-proliferative effects, while the expression of Smad2/3 proteins that promote proliferation is abnormally upregulated. This imbalance ultimately drives the abnormal proliferation of small pulmonary arterial smooth muscle cells and induces pulmonary vascular remodeling[44]. Sotatercept is an activin receptor type IIA (ActRIIA)-Fc fusion protein that can neutralize abnormally elevated activin-like ligands in PAH, regulate Smad2/3 signaling, and exert anti-proliferative, pro-apoptotic, and anti-inflammatory effects[44]. Approved for PAH treatment in 2024, sotatercept includes CTD-PAH in its indication scope, providing a new option for CTD-PAH treatment. Multiple studies have been published before and after its approval. The STELLAR trial is a randomized, double-blind trial designed to compare the efficacy of adding sotatercept versus placebo on the basis of dual or triple PAH-specific therapy (sotatercept group n=163, placebo group n=160; CTD-PAH patients accounting for 17.8%). The results showed that compared with the placebo group, patients in the sotatercept group had significantly improved exercise tolerance, and the risk of clinical worsening or death was reduced by 84%. The most common adverse events were bleeding events (21.5%, mostly non-severe epistaxis and gingival bleeding), telangiectasia (10.4%), thrombocytopenia (6.1%), increased hemoglobin levels (5.5%), and elevated blood pressure (3.7%) [45]. Based on the STELLAR trial, McLaughlin et al. used a population health model to evaluate the potential long-term clinical impact of sotatercept and found that adding sotatercept to background therapy (monotherapy, dual, or triple PAH targeted therapy) can prolong the life expectancy of PAH patients by approximately 3 times, while reducing the use of intravenous prostacyclins, the number of PAH-related hospitalizations, and the need for lung/cardiopulmonary transplantation [46]. In addition, the interim analysis of the SOTERIA study supports a favorable long-term benefit-risk ratio of sotatercept in PAH patients, with controllable safety and durable efficacy. This study included 426 PAH patients, with CTD-PAH accounting for 17.6% [47].

The approval of sotatercept represents a milestone breakthrough in PAH treatment. Its mechanism of reversing pulmonary vascular remodeling has rewritten the traditional treatment paradigm, and it has achieved good clinical efficacy in current applications. However, due to limited sample size and study duration, its long-term safety and prognostic impact on CTD-PAH patients still need further verification, and there are no large-scale cohort studies specifically targeting CTD-PAH, requiring more clinical evidence to support its use.

4. Other Targeted Therapeutic Agents

In addition to the aforementioned drugs, promising targeted therapeutic agents for CTD-PAH currently under investigation include tyrosine kinase receptor antagonists acting on platelet-derived growth factor receptors (PDGFR) and the immune-targeted drug rituximab.

4.1. Tyrosine Kinase Receptor Antagonists

Receptor tyrosine kinases (RTKs) are core components of the platelet-derived growth factor (PDGF) pathway, which plays a key role in regulating cell proliferation. Tyrosine kinase receptor inhibitors can exert therapeutic effects on PAH by inhibiting this pathway. Drugs currently under research for PAH treatment include imatinib [48]and seralutinib[49]. A previous multicenter, randomized, double-blind, placebo-controlled phase II trial by Ghofrani et al. [50] and the phase III IMPRES study (n=202) [51]initially demonstrated the potential of imatinib to improve PVR and 6MWD in PAH patients, but the effects were modest. Recently, an open-label, single-arm, Bayesian continuous reassessment model (CRM)-driven phase II clinical trial by Rothman et al. [52] involving 17 PAH patients showed that oral imatinib at a dose of 200 mg/d as an add-on therapy was well-tolerated, significantly improved hemodynamics with durable efficacy, but did not significantly change 6MWD. Seralutinib is an inhaled tyrosine kinase receptor inhibitor specifically developed for PAH[53]. A study involving 86 PAH patients (WHO functional class II or III) evaluated the efficacy of inhaled seralutinib. These patients were randomly assigned to receive seralutinib or placebo in a 1:1 ratio while continuing their original PAH treatment[54]. The results showed that the drug was well-tolerated, significantly reduced PVR in patients, but only improved 6MWD by 6.5 meters. The TORREY open-label extension (OLE) study further verified the long-term safety and efficacy of inhaled seralutinib in PAH patients [55]. The above studies initially demonstrated the potential value of tyrosine kinase receptor antagonists in PAH treatment, but they generally suffer from small sample sizes. Even contradictorily, a case report showed that a female adult developed PAH after treatment with this class of drugs[56]. Research on their use in CTD-PAH treatment is even rarer; CTD-PAH patients were only included in small numbers in studies such as the IMPRES study [51] and TORREY study[55] along with other PAH patients, lacking sufficient statistical power. In summary, the efficacy and adverse reactions of this class of drugs remain unclear, and more targeted clinical studies are needed for verification in the future.

4.2. Rituximab

Rituximab is a CD20-targeted monoclonal antibody that depletes B cells, commonly used in the treatment of tumors and autoimmune diseases. It is well-known that B cell immunity plays an important role in the pathogenesis of CTD (such as SSc and SLE), and PAH itself is associated with autoimmune dysregulation. A multicenter, double-blind, randomized, placebo-controlled phase II study by Zamanian et al. [57] included 57 SSc-PAH patients receiving background PAH treatment. The results showed that the primary endpoint of change in 6MWD at 24 weeks did not reach statistical significance, but a pre-specified secondary endpoint analysis indicated that rituximab significantly improved exercise tolerance in patients (mean improvement of 25.1 meters after placebo adjustment, p=0.03). A systematic review by Amany Touil et al. [58] (n=7) evaluated the efficacy and safety of rituximab in the treatment of CTD-PAH. This review included 6 studies on rituximab treatment for CTD-PAH (including 2 prospective studies), with female patients accounting for the majority (85.9%). The average number of rituximab infusions was 4.2, and the mean follow-up duration was 18.3 months. The results showed that both clinical and auxiliary examination indicators of patients were improved with good tolerability, suggesting that rituximab has potential efficacy and safety in the treatment of CTD-PAH. However, relevant research is currently limited and lacks convincing evidence, warranting further investigations in the future.

5. Combination Therapy and Risk Stratification-based Treatment

The internationally recognized PAH treatment strategy emphasizes early combination therapy based on risk stratification. For low-risk and medium-risk PAH patients, initial dual therapy, i.e., combination of endothelin receptor antagonist (ERA) and phosphodiesterase 5 inhibitor (PDE5i), is recommended. For high-risk patients, it is recommended to add parenterally or subcutaneously administered prostacyclin analogues to the above dual therapy regimen to form "triple therapy" [1]. A large body of clinical trial evidence has shown that standardized initial combination therapy can significantly reduce mortality risk and improve long-term prognosis. The combination therapy and risk stratification-based treatment strategies for CTD-PAH are basically consistent with those for I/HPAH according to the 2022 ESC/ERS guidelines [1], and will not be repeated in this review. It is worth noting that unlike traditional targeted therapies that expand narrowed blood vessels to reduce pulmonary arterial pressure, the emerging targeted drug sotatercept has the core advantage of reversing vascular remodeling. It is expected to rewrite the pattern of combination therapy for CTD-PAH in the future, and its combination regimens need to be explored in more clinical studies.

6. Outlook and Conclusion

CTD-PAH is characterized by immune dysregulation-mediated pulmonary vascular remodeling with extremely poor prognosis. In recent years, its treatment has evolved from the traditional three major vasodilatory pathways to a diversified model of "immune regulation + vascular repair". The approval of sotatercept marks the entry into a new stage of reversing vascular remodeling, and drugs such as rituximab have also shown potential efficacy. However, most emerging therapies lack sufficient clinical evidence, and there is a paucity of large-scale studies specifically targeting CTD-PAH. Issues such as precise stratification remain to be addressed. In the future, relying on technological innovation and multidisciplinary collaboration, advancing early screening and combination therapy is expected to achieve precise intervention and improve the prognosis of patients.

References

[1] Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022; 43 (38): 3618-731.

[2] Southgate L, Machado RD, Gräf S, Morrell NW. Molecular genetic framework underlying pulmonary arterial hypertension. Nat Rev Cardiol. 2020; 17 (2): 85-95.

[3] Yuan K, Shamskhou EA, Orcholski ME, et al. Loss of endothelium-derived wnt5a is associated with reduced pericyte recruitment and small vessel loss in pulmonary arterial hypertension. Circulation. 2019; 139 (14): 1710-24.

[4] Lau EMT, Giannoulatou E, Celermajer DS, Humbert M. Epidemiology and treatment of pulmonary arterial hypertension. Nat Rev Cardiol. 2017; 14 (10): 603-14.

[5] Zhang C, Ding H, Li J, et al. Epidemiology, disease burden of pulmonary arterial hypertension in china: a systematic literature review. Respir Med. 2025; 240: 108007.

[6] Stacher E, Graham BB, Hunt JM, et al. Modern age pathology of pulmonary arterial hypertension. Am J Respir Crit Care Med. 2012; 186 (3): 261-72.

[7] He X, Fang J, Gong M, et al. Identification of immune-associated signatures and potential therapeutic targets for pulmonary arterial hypertension. J Cell Mol Med. 2023; 27 (23): 3864-77.

[8] Heukels P, Corneth OBJ, van Uden D, et al. Loss of immune homeostasis in patients with idiopathic pulmonary arterial hypertension. Thorax. 2021; 76 (12): 1209-18.

[9] Mocumbi A, Humbert M, Saxena A, et al. Pulmonary hypertension. Nat Rev Dis Primers. 2024; 10 (1): 1.

[10] Boucly ANS, Gerges C, Savale L, et al. Pulmonary arterial hypertension. Presse Med. 2023; 52 (3): 104168.

[11] Condon DF, Agarwal S, Chakraborty A, et al. Novel mechanisms targeted by drug trials in pulmonary arterial hypertension. Chest. 2022; 161 (4): 1060-72.

[12] Pluchart HLN, Khouri C, Blaise S, Roustit M, Cracowski JL. Targeting the prostacyclin pathway: beyond pulmonary arterial hypertension. Trends Pharmacol Sci. 2017; 38 (6): 512-23.

[13] Cansu DNSD, Korkmaz C. Pulmonary hypertension in connective tissue diseases: epidemiology, pathogenesis, and treatment. Clin Rheumatol. 2023; 42 (10): 2601-10.

[14] Zeng C, Liu J, Zheng X, Hu X, He Y. Prostaglandin and prostaglandin receptors: present and future promising therapeutic targets for pulmonary arterial hypertension. Respir Res. 2023; 24 (1): 263.

[15] Dhoble S, Patravale V, Weaver E, Lamprou DA, Patravale T. Comprehensive review on novel targets and emerging therapeutic modalities for pulmonary arterial hypertension. Int J Pharm. 2022; 621: 121792.

[16] Feenstra J, Hopkins P, Trotter M, O'Brien K. Effectiveness of epoprostenol in the management of pulmonary arterial hypertension: findings of an australian retrospective chart review. Intern Med J. 2020; 50 (11): 1377-84.

[17] Tello K, Delcroix M, Pausch C, et al. Add-on therapy with parenteral prostacyclin analogues in patients with pulmonary arterial hypertension: insights from the COMPERA registry. J Heart Lung Transplant. 2026; 45 (2): 284-8.

[18] Bruni C, Cometi L, Gigante A, Rosato E, Matucci-Cerinic M. Prediction and primary prevention of major vascular complications in systemic sclerosis. Eur J Intern Med. 2021; 87: 51-8.

[19] Gaine S, Chin K, Coghlan G, et al. Selexipag for the treatment of connective tissue disease-associated pulmonary arterial hypertension. Eur Respir J. 2017; 50 (2).

[20] Gaine S, Escribano-Subias P, Muller A, et al. Selexipag in patients with pulmonary arterial hypertension associated with connective tissue disease (PAH-CTD): real-world experience from EXPOSURE. Pulm Circ. 2024; 14 (3): e12403.

[21] Burger CD, Tang W, Tsang Y, Panjabi S. Early addition of selexipag to double therapy for pulmonary arterial hypertension. JAMA Netw Open. 2024; 7 (9): e2434691.

[22] Barberà J, Jansa P, Klings E, et al. Ralinepag phase II open-label extension study in patients with pulmonary arterial hypertension. Adv Ther. 2024; 41 (3): 1062-74.

[23] Torres F, Farber H, Ristic A, et al. Efficacy and safety of ralinepag, a novel oral IP agonist, in PAH patients on mono or dual background therapy: results from a phase 2 randomised, parallel group, placebo-controlled trial. Eur Respir J. 2019; 54 (4).

[24] Lázár ZF, Mészáros M, Bikov A. The nitric oxide pathway in pulmonary arterial hypertension: pathomechanism, biomarkers and drug targets. Curr Med Chem. 2020; 27 (42): 7168-88.

[25] Benza RL, Grünig E, Sandner P, Stasch JP, Simonneau GR. The nitric oxide-soluble guanylate cyclase-cGMP pathway in pulmonary hypertension: from PDE5 to soluble guanylate cyclase. Eur Respir Rev. 2024; 33 (171).

[26] Zhao J, Wang Q, Deng X, et al. The treatment strategy of connective tissue disease associated pulmonary arterial hypertension: evolving into the future. Pharmacol Ther. 2022; 239: 108192.

[27] Wang RR, Yuan TY, Wang JM, et al. Immunity and inflammation in pulmonary arterial hypertension: from

pathophysiology mechanisms to treatment perspective. Pharmacol Res. 2022; 180: 106238.

[28] Favoino E, Prete M, Liakouli V, et al. Idiopathic and connective tissue disease-associated pulmonary arterial hypertension (PAH): similarities, differences and the role of autoimmunity. Autoimmun Rev. 2024; 23 (4): 103514.

[29] Cianciarulo C, Nguyen TH, Zacharias A, Standen N, Tucci J, Irving H. Analysis of phosphodiesterase-5 (PDE5) inhibitors in modulating inflammatory markers in humans: a systematic review and meta-analysis. Int J Mol Sci. 2025; 26 (15).

[30] Jin YS, Yang B, Ding L, Jiang B. [Mechanism of vitamin d deficiency involvement in the development of pulmonary arterial hypertension related to monocrotaline-induced connective tissue disease in rats]. Zhonghua Yi Xue Za Zhi. 2024; 104 (43): 3972-9.

[31] Adão R, Barreira B, Paternoster E, et al. Vitamin d as an add-on therapy to phosphodiesterase-5 inhibitor in experimental pulmonary arterial hypertension. Am J Physiol Lung Cell Mol Physiol. 2025; 328 (2): L253-9.

[32] Hoeper MM, Al-Hiti H, Benza RL, et al. Switching to riociguat versus maintenance therapy with phosphodiesterase-5 inhibitors in patients with pulmonary arterial hypertension (REPLACE): a multicentre, open-label, randomised controlled trial. Lancet Respir Med. 2021; 9 (6): 573-84.

[33] Humbert M, Hassoun PM, Chin KM, et al. MK-5475, an inhaled soluble guanylate cyclase stimulator, for treatment of pulmonary arterial hypertension: the INSIGNIA-PAH study. Eur Respir J. 2024; 64 (5).

[34] Galiè N, Müller K, Scalise AV, Grünig E. PATENT PLUS: a blinded, randomised and extension study of riociguat plus sildenafil in pulmonary arterial hypertension. Eur Respir J. 2015; 45 (5): 1314-22.

[35] Motte S, Mcentee K, Naeije R. Endothelin receptor antagonists. Pharmacol Ther. 2006; 110 (3): 386-414.

[36] Fischer A, Denton CP, Matucci-Cerinic M, et al. Ambrisentan response in connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH) - a subgroup analysis of the ARIES-e clinical trial. Respir Med. 2016; 117: 254-63.

[37] Li M, Jing ZC, Li Y, et al. Efficacy and safety of ambrisentan in chinese patients with connective tissue disease-pulmonary arterial hypertension: a post-hoc analysis. BMC Cardiovasc Disord. 2020; 20 (1): 339.

[38] Kuang HY, Li Q, Du HA, Chen M, Yin YH. Efficacy and safety of long-term oral bosentan in different types of pulmonary arterial hypertension: a systematic review and meta-analysis. Am J Cardiovasc Drugs. 2021; 21 (2): 181-91.

[39] Dong S, Guo X, Wang H, Sun C. Liver injury due to endothelin receptor antagonists: a real-world study based on post-marketing drug monitoring data. Ther Adv Respir Dis. 2024; 18: 17534666231223606.

[40] Gebreselassie A, Aduli F, Howell CD. Rheumatologic diseases and the liver. Clin Liver Dis. 2019; 23 (2): 247-61.

[41] Pulido TS, Adzerikho I, Channick RN, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. N Engl J Med. 2013; 369 (9): 809-18.

[42] Souza RRO, Delcroix M, Galié N, et al. Long-term safety, tolerability and survival in patients with pulmonary arterial hypertension treated with macitentan: results from the SERAPHIN open-label extension. Adv Ther. 2022; 39 (9): 4374-90.

[43] Channick R, Chin KM, Mclaughlin VV, et al. Macitentan in pulmonary arterial hypertension associated with connective tissue disease (CTD-PAH): real-world evidence from the combined OPUS/OrPHeUS dataset. Cardiol Ther. 2024; 13 (2): 315-39.

[44] Adu-Amankwaah J, Shi Y, Song H, et al. Signaling pathways and targeted therapy for pulmonary hypertension. Signal Transduct Target Ther. 2025; 10 (1): 207.

[45] Hoeper MM, Badesch DB, Ghofrani HA, et al. Phase 3 trial of sotatercept for treatment of pulmonary arterial hypertension. N Engl J Med. 2023; 388 (16): 1478-90.

[46] Mclaughlin V, Alsumali A, Liu R, et al. Population health model predicting the long-term impact of sotatercept on morbidity and mortality in patients with pulmonary arterial hypertension (PAH). Adv Ther. 2024; 41 (1): 130-51.

[47] Preston IR, Badesch D, Ghofrani HA, et al. A long-term follow-up study of sotatercept for treatment of pulmonary arterial hypertension: interim results of SOTERIA. Eur Respir J. 2025; 66 (1).

[48] Ten Freyhaus H, Dumitrescu D, Berghausen E, Vantler M, Caglayan E, Rosenkranz S. Imatinib mesylate for the treatment of pulmonary arterial hypertension. Expert Opin Investig Drugs. 2012; 21 (1): 119-34.

[49] Pullamsetti SS, Sitapara R, Osterhout R, et al. Pharmacology and rationale for seralutinib in the treatment of pulmonary arterial hypertension. Int J Mol Sci. 2023; 24 (16).

[50] Ghofrani HA, Morrell NW, Hoeper MM, et al. Imatinib in pulmonary arterial hypertension patients with inadequate response to established therapy. Am J Respir Crit Care Med. 2010; 182 (9): 1171-7.

[51] Hoeper MM, Barst RJ, Bourge RC, et al. Imatinib mesylate as add-on therapy for pulmonary arterial hypertension: results of the randomized IMPRES study. Circulation. 2013; 127 (10): 1128-38.

[52] Rothman AMK, Villar SS, Middleton J, et al. Positioning imatinib for pulmonary arterial hypertension: a dose-finding phase 2 study. Am J Respir Crit Care Med. 2025; 211 (6): 1018-27.

[53] Galkin A, Sitapara R, Clemons B, et al. Inhaled seralutinib exhibits potent efficacy in models of pulmonary arterial hypertension. Eur Respir J. 2022; 60 (6).

[54] Frantz RP, Mclaughlin VV, Sahay S, et al. Seralutinib in adults with pulmonary arterial hypertension (TORREY): a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Respir Med. 2024; 12 (7): 523-34.

[55] Sitbon O, Sahay S, Escribano Subías P, et al. Seralutinib for the treatment of pulmonary arterial hypertension in adults: TORREY open-label extension study. Adv Ther. 2025; 42 (10): 5104-23.

[56] Carbonera S, Scelsi L, Greco A, et al. Pulmonary arterial hypertension onset in an adult woman with a TBX4 likely pathogenic variant following imatinib administration: a case report. Am J Med Genet A. 2025; 197 (11): e64178.

[57] Zamanian RT, Badesch D, Chung L, et al. Safety and efficacy of b-cell depletion with rituximab for the treatment of systemic sclerosis-associated pulmonary arterial hypertension: a multicenter, double-blind, randomized, placebo-controlled trial. Am J Respir Crit Care Med. 2021; 204 (2): 209-21.

[58] Touil A, Bouden S, Maazaoui S, et al. Rituximab treatment for connective tissue diseases associated-pulmonary hypertension: a systematic literature review. Expert Rev Respir Med. 2025: 1-8.