

Treating Inflammation Associated with Pulmonary Hypertension: An Overview of the Literature

Hugo Hyung Bok Yoo ¹, Flávia Luiza Marin ²

¹Department of Pulmonology, Botucatu Medical School of São Paulo State University (UNESP), Botucatu, São Paulo, Brazil; ²Department of Internal Medicine, State University of Western Paraná (UNIOESTE), Francisco Beltrão, Paraná, Brazil

Correspondence: Hugo Hyung Bok Yoo, Email hugo.yoo@unesp.br

Abstract: Pulmonary hypertension (PH) comprises five groups of serious clinical entities characterized by pulmonary artery vasoconstriction and vascular remodeling leading to right heart failure and death. In addition to vascular remodeling, recruitment and exaggerated accumulation of several perivascular inflammatory cells is also observed, including macrophages, monocytes, T and B-lymphocytes, dendritic cells and mast cells distributed in pulmonary perivascular spaces and around remodeling pulmonary vessels. Current pulmonary arterial hypertension (PAH)-targeted therapies aim to improve functional capacity, pulmonary hemodynamic conditions, and delay disease progression. Nevertheless, PAH remains incurable, with a poor prognosis and is often refractory to drug therapy, highlighting the need for further research. In the last three decades, the best pathophysiological understanding of PAH has allowed for progression from a disease of little-known pathogenesis, without specific and effective therapy to expanding the arsenal of drugs on a cellular, genetic and molecular basis. This article provides an overview on current knowledge and progress in recent advances in pharmacological therapy in PAH.

Keywords: pulmonary arterial hypertension, inflammation, treatment

Definition and Classification of Pulmonary Hypertension

Pulmonary hypertension (PH) is a life-threatening and progressive disease of different conditions characterized by an increase of the mean pulmonary arterial pressure (mPAP) ≥ 20 mmHg that results in right heart dysfunction.^{1,2}

PH is classified into five separate groups based on the combination of hemodynamic parameters, clinical presentation, similar pathophysiology mechanisms and therapeutic management. Pulmonary arterial hypertension (PAH) (Group 1), which is a precapillary PH (pulmonary wedge pressure ≤ 15 mmHg) includes idiopathic, heritable, drug and toxin-induced PAH and associated forms of PAH such as connective tissue disease, portal hypertension, congenital heart disease, human immunodeficiency virus (HIV) and schistosomiasis. The remaining 4 groups of PH are secondary to other conditions and are usually referred to as secondary PH. PH due to left heart diseases (Group 2) which is a postcapillary PH (pulmonary wedge pressure > 15 mmHg); PH due to lung diseases and/or hypoxemia (Group 3); PH due to pulmonary artery obstructions (Group 4) and PH due to unclear and/or multifactorial mechanisms (Group 5) (Table 1).²

The management of pulmonary arterial hypertension (PAH) has significantly improved in recent decades with the proposal of more sensitive diagnoses and more robust risk stratification.¹ As a result, 1-year survival rates have increased from 65% in the 1980s to 86% to 90%, and average long-term survival has increased from 2.8 years to 6 years.³ The heterogeneity in the PH etiology and multifactorial pathophysiology has stimulated research focusing on understanding the pathophysiology of the disease at cellular and genetic levels. This may provide prospects for the development of new drugs that can prevent or reverse pulmonary vascular remodeling.³

Overview of Inflammation and Immune Mechanisms in PH

The first studies reporting on inflammation in pathophysiology of PH appeared over 40 years ago, but more in-depth studies began around 20 years ago.⁴ Acute inflammation is the primary adaptive response of the organism to harmful

Table I Updated Clinical Classification of Pulmonary Hypertension**Group 1: PAH**

- 1.1 Idiopathic PAH
- 1.2 Heritable PAH
- 1.3 Drug and toxin-induced PAH
- 1.4 PAH associated with:
 - 1.4.1 Connective tissue disease
 - 1.4.2 HIV infection
 - 1.4.3 Portal hypertension
 - 1.4.4 Congenital heart disease
 - 1.4.5 Schistosomiasis
- 1.5 PAH long-term responders to calcium channel blockers
- 1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement
- 1.7 Persistent PH of the newborn syndrome

Group 2: PH due to left heart disease

- 2.1 PH due to heart failure with preserved LVEF
- 2.2 PH due to heart failure with reduced LVEF
- 2.3 Valvular heart disease
- 2.4 Congenital/acquired cardiovascular conditions leading to postcapillary PH

Group 3: PH due to lung diseases and/or hypoxia

- 3.1 Obstructive lung disease
- 3.2 Restrictive lung disease
- 3.3 Other lung disease with mixed restrictive/obstructive pattern
- 3.4 Hypoxia without lung disease
- 3.5 Developmental lung disorders

Group 4: PH due to pulmonary artery obstructions

- 4.1 Chronic thromboembolic PH
- 4.2 Other pulmonary artery obstructions

Group 5: PH with unclear and/or multifactorial mechanisms

- 5.1 Hematological disorders
- 5.2 Systemic and metabolic disorders
- 5.3 Others

Abbreviations: LVEF, left ventricular ejection; PAH, pulmonary arterial hypertension; PCH, pulmonary capillary hemangiomatosis; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease. Data from Simonneau et al.²

stimuli. Chronic inflammation, by contrast, is a prolonged, maladaptive fibrosis and immune dysfunction are observed in several types of PH, such as Idiopathic PAH and PAH associated with connective tissue diseases (for example, systemic lupus erythematosus (SLE) and systemic sclerosis) and secondary to infections (for example, HIV and schistosomiasis), but it is true that inflammatory cells are found in almost all forms of severe PH.^{5,6} Thus, chronic inflammation can develop due to infection or antigen persistence, persisting tissue damage, or inability of endogenous anti-inflammatory mechanisms that drive the resolution of inflammation. It is noteworthy that, regardless of the cause, inflammation likely advanced as an adaptive response to restore homeostasis.⁴⁻⁶

There may be some pathobiological concepts that apply to all forms of severe PAH; for example, the concept of an overactive inflammatory response in “wound healing gone awry” If so, then inflammation in PAH can be understood as part of the biology of wound healing.⁴

The known pathophysiology of PAH, which includes the mechanical concepts of pressure, flow, shear stress, RV wall tension and impedance, must be integrated with the new pathobiological concepts of cell injury and repair, and interactions of complex multicellular systems. In addition, precursor and bone marrow-derived stem cells and resident pulmonary vascular stem cells should also be considered active participants in the pulmonary vascular “wound healing gone awry” process.^{4,7} This model is based on the unusual lung blood flow. Regional blood flow abnormalities underlie the pulmonary vascular remodeling that causes further arrangement of the regional blood flow, sustaining a cycle of cell

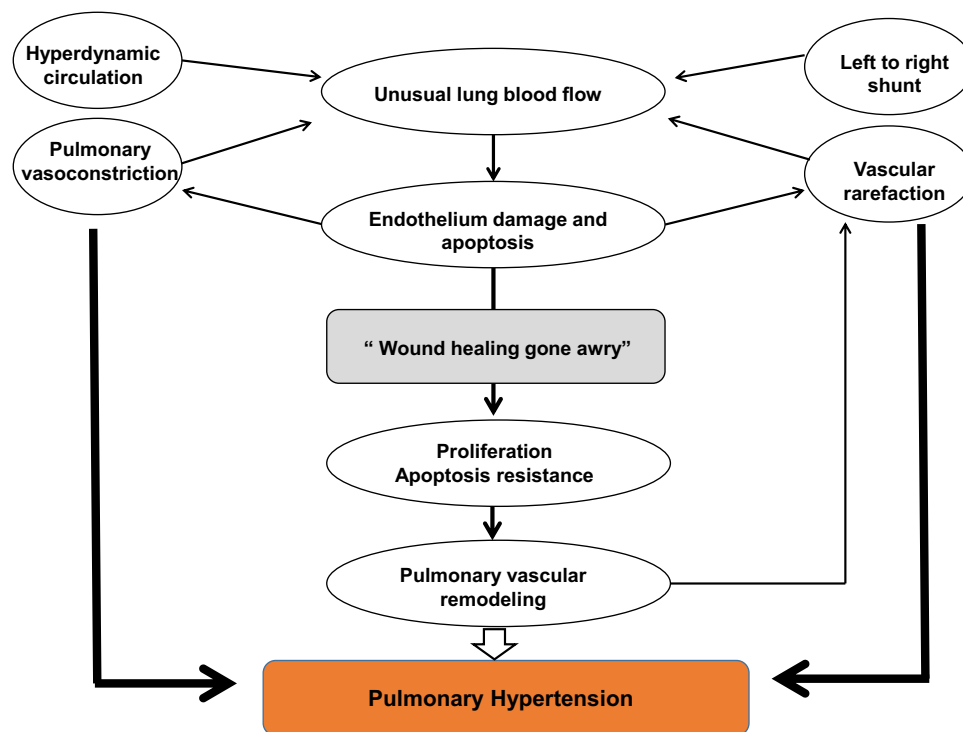


Figure 1 Hemodynamic integration and cell injury and repair that illustrate the cardiopulmonary condition of severe pulmonary arterial hypertension (PAH). Data from Voelkel et al.⁷

death and cell proliferation. Vascular rarefaction occurs in the form of pruning of small pulmonary vessels and, in the right ventricle, in the form of myocardial capillary rarefaction (Figure 1).⁷

Nonetheless, it has gradually become clearer that the PH pathobiology and the chronic persistent inflammation process are common to all forms. It is widely accepted that inflammation is a powerful pathological driver of susceptibility and progression of vascular remodeling in PAH nowadays.⁸

PAH is characterized by increased pulmonary vascular resistance due to irreversible remodeling and occlusion of the pulmonary vessels with vasoconstriction resulting in right heart failure and early death.^{5,8} This process is characterized by a medial hypertrophy/hyperplasia, intimal and adventitial fibrosis, in situ thrombosis, and plexiform lesions.^{6,8}

Moreover, PAH can present autoimmune features such as high serum levels of anti-nuclear, anti-fibroblast, and anti-endothelial cell antibodies. Recruitment and exaggerated accumulation of several perivascular inflammatory cells is also observed. Macrophages, monocytes, T- and B-lymphocytes, cytotoxic and helper T cells, regulatory T-cell (Treg), natural killer cells, dendritic cells and mast cells can be distributed in pulmonary perivascular spaces and around plexiform lesions of PAH.⁹ Thus, the perivascular inflammation could act as a driving force in the development of subsequent medial and intimal remodeling.¹⁰ Recruited inflammatory cells release some mediators that can directly modify the vessel microenvironment and recruit additional circulating inflammatory cells that worsen disease progression.^{10,11} Therefore, it is possible that perivascular pulmonary inflammation represents a pivotal link between adventitial activation and vascular changes in response to a variety of stimuli.¹²

The adaptive immune response activates and generates an organized structure involving T and B-lymphocytes around a germinal center, characterized by pulmonary lymphoid neogenesis. Furthermore, pulmonary lymphoid neogenesis can be found in idiopathic PAH. It have been identified tertiary lymphoid tissues ranging from small lymphoid aggregates to large lymphocyte accumulations similar to highly organized lymphoid follicles. This could supply a structural basis for a local adaptive immune response observed in idiopathic PAH lungs.¹³

Inflammatory cells accumulate around the vascular walls and raise peripheral blood inflammatory cells simultaneously.¹ The levels of circulating proinflammatory cytokines (interleukin (IL)-1, IL-6, tumor necrosis factor

(TNF- α), and chemokines (fractalkine) are increased in PAH and directly associated with modulating proliferation, differentiation, and of pulmonary vascular cells migration.^{5,8} IL-1 plays an essential role in vascular remodeling. It regulates the secretion of osteoprotegerin by the pulmonary artery smooth muscle cells (PASMCs) (Figure 2).^{9,11,14}

IL-6 is a pleiotropic cytokine whose levels are elevated in the serum and lungs in PAH patients. Those high levels induce pericyte migration and vascular remodeling by activation of signal transducer, activator of transcription 3 (STAT3) and Krüppel-like factor 5 (KLF). TNF- α contributes to the PASMC apoptosis-resistant phenotype by inhibiting pyruvate dehydrogenase (PDH), which participates to mitochondrial membrane hyperpolarization and nuclear factor of activated T cells (NFAT) activation.^{11,12,14}

In an experimental study, TNF- α was identified to potentiate pulmonary vasoconstriction and increase pulmonary vascular reactivity.¹⁵ The chemokine fractalkine, a chemoattractant for monocytes and T-lymphocytes, is expressed by

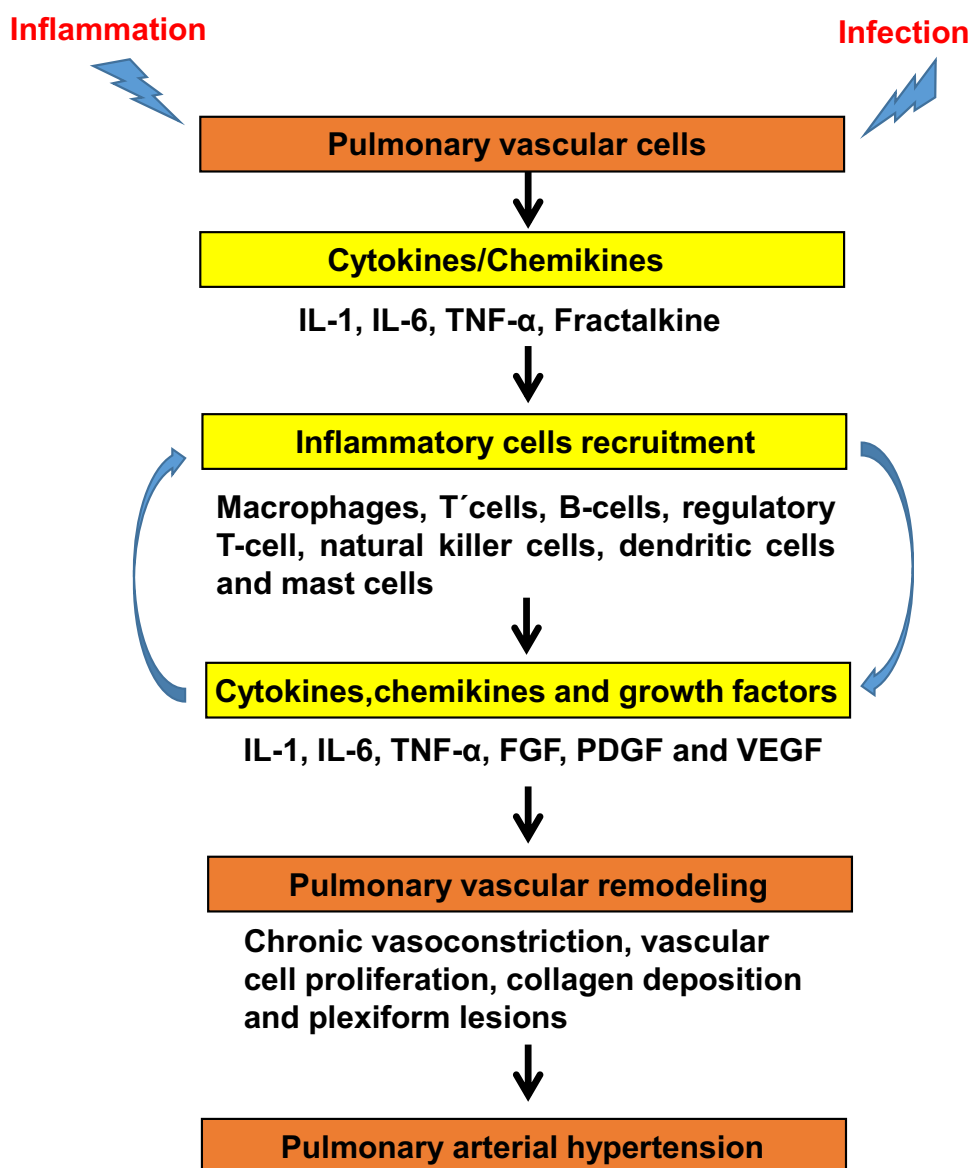


Figure 2 Schematic illustration of inflammation and infection-mediated vascular remodeling: upon stimulation by infection and/or inflammation, lung vascular cells produce and release inflammatory mediators (chemokines and cytokines), thereby recruiting the inflammatory cells. Under the coordination of inflammatory mediators, inflammatory cells can promote the release of cytokines and chemokines, which leads to chronic vasoconstriction, vascular remodeling by vascular cell proliferation, collagen deposition and plexiform lesions. The progressive process causes pulmonary arterial hypertension.

Abbreviations: IL, interleukin; TNF- α , tumor necrosis factor- α ; FGF, fibroblast growth factor; PDGF, platelet-derived growth factor; VEGF, vascular endothelial growth factor.

inflammatory cells surrounding pulmonary vasculatures lesions (plexiform lesions) and induced PASMC proliferation in PAH experimental models^{9,14} Thus, fractalkine may act as a growth factor for pulmonary artery smooth cells.¹⁴

Likewise, in PAH with marked worsening of right ventricular dysfunction, there is overexpression of several cytokines and chemokines with increased activity of inflammatory cells in the myocardium and activation of cardiomyocytes and fibroblasts. Thus, treating the underlying inflammatory condition may moderate the associated PAH.⁴

Bone morphogenetic protein receptor type 2 (BMPR2), a member of the TGF- β superfamily, is considered as a major factor underlying heritable genes in developing PAH. BMPR2 mutation carriers are related to susceptibility to PAH, identified in hereditary PAH, younger patients and in the most severe form of PAH. It is associated with right ventricular dysfunction, higher mortality and poor prognosis than those with normal BMPR2.^{1,16}

Due to its incomplete penetration, about 80% of BMPR2 mutation carriers might not develop PAH.¹ This fact has led to speculation that the combination of the genetic defect combined with a lung-specific trigger might be necessary for the disease to be evident.¹⁷

BMPR2 plays an important role in regulating the barrier function of pulmonary artery endothelial cells (PAECs), demonstrated by increased monolayer permeability and increased recruitment identified in cells with reduced BMPR2 expression.¹⁸ Therefore, a reduction in BMPR2 expression and the resultant reduction in natural endothelial barrier function may predispose to inflammation-induced pulmonary vascular damage.¹⁸ It has been shown that there is an important feedback loop between BMPR2 and IL-6. A disordered BMPR2 signaling in fibroblasts can cause cytokine dysregulation and promotes an exaggerated inflammatory response in PAH progression. Besides, cytokines such as IL-6 may directly affect the expression of BMPR2.^{9,10,18}

Current Medical Treatment Options in PAH

Only a small group of patients with Idiopathic PAH (6%) who appear to have a favorable response to acute vasodilator testing at the time of right cardiac catheterization may have long-term benefit from calcium channel blockers (CCB) such as nifedipine, diltiazem and amlodipine. Patients with no acute vasodilation response should be not treated with CCB.¹

Currently, four classes of PAH-specific therapeutic drugs are available: prostacyclin (epoprostenol) and its analogues (treprostinil, iloprost, beraprost) which have been modified for longer half-life; selective IP prostacyclin-receptor agonist (selexipag); endothelin receptor antagonists (bosentan, ambrisentan, macitentan); phosphodiesterase type 5 inhibitors (PDE5i) (sildenafil, tadalafil); and soluble guanylate cyclase stimulators (riociguat). Treatment focuses on three main pathways: the endothelin (ET) pathway, the nitric oxide (NO)/cyclic guanosine monophosphate (cGMP) pathway, and the prostacyclin pathway (Table 2). All of these drugs act on endothelial dysfunction, aiming to promote vasodilation and

Table 2 Classes of Therapeutic Drugs Specific to PAH

	Endothelin Receptor Antagonists	PDE5 Inhibitors	Prostacyclin Analogues	Prostacyclin Receptor Agonists	sGC Stimulators
Generic names	Bosentan, ambrisentan, macitentan	Sildenafil, tadalafil	Epoprostenol, Iloprost, treprostinil, beraprost	Selexipag	Riociguat
Route of administration	Oral	Oral	Intravenous, inhaled, subcutaneous, oral	Oral	Oral
Common side effects	Hepatotoxicity, peripheral edema, nasal congestion, nasopharyngitis, headache, anemia	Headache, dyspepsia, diarrhea, myalgia, flushing, epistaxis	Central venous access infection, or blockage, cough, headache, flushing, jaw pain	Headache, nasopharyngitis, edema, nausea, anemia, jaw pain,	Headache, dyspepsia, peripheral edema, dizziness, hypotension

Abbreviations: PAH, pulmonary arterial hypertension; PDE5, phosphodiesterase type 5; sGC, soluble guanylate cyclase. Data from Galie et al.¹

delay the process of vascular remodeling. It is noteworthy that these molecules also present immunomodulatory properties that could participate in their efficacy.^{1,11,19}

Since inflammation plays a key role in the global pathophysiology of various forms of PH, it would be sensible to introduce into the treatment strategy drugs that modify inflammation and perhaps autoimmunity. With the exception of prostacyclin, all drugs currently available to treat PH have limited anti-inflammatory properties.⁴

Prostacyclin is produced by the metabolism of arachidonic acid in the endothelium and induces the production of cyclic adenosine monophosphate (cAMP), causing vasodilation and has antiproliferative effects as well. Prostacyclin signaling also suppresses platelet aggregation and endothelial cell proliferation, which may moderate intravascular thrombosis.¹⁹

Prostacyclin (epoprostenol) and its analogues target IP receptors (treprostinil, iloprost, beraprost), elevate intracellular cAMP, and suppresses Th-2 cell-mediated inflammatory responses, increasing the production of the anti-inflammatory cytokine IL-10.²⁰ In addition, prostacyclin inhibits platelet aggregation and lymphocyte adhesion to endothelial cells.^{19,20} Prostacyclin signaling can be stimulated by administration of a prostacyclin receptor agonist or a prostacyclin derivative.¹⁹ It is not yet known whether prostacyclin also exhibits anti-inflammatory properties in dysfunction of the right ventricle of patients with severe PAH.^{4,20}

Epoprostenol (synthetic prostacyclin) has a short half-life of 3–5 minutes and is administered by an infusion pump and a permanent tunneled catheter. Epoprostenol improves symptoms, exercise capacity and haemodynamic parameters and it is the only drug associated with reduced mortality.¹

Treprostinil is a tricyclic benzidine analogue of epoprostenol that is chemically stable enough to be administered at room temperature. Those characteristics allow administration of both routes: intravenous and subcutaneous.^{1,21}

Iloprost is a chemically stable prostacyclin analogue available for intravenous, oral or aerosol administration. Repetitive daily inhaled iloprost was compared with placebo inhalation in patients with PAH and chronic thromboembolic pulmonary hypertension (CTEPH).²² The study showed an increase in exercise capacity and improvement in symptoms, pulmonary vascular resistance (PVR) and clinical events in enrolled patients.²² A second study of 60 patients already treated with bosentan showed an increase in exercise capacity in subjects randomized to the addition of inhaled iloprost compared to placebo.²³ More importantly, prostacyclin analogues associated with endothelin receptor antagonists reduce endothelial cell activation, inducing vasodilatation and reducing vascular cell growth in PAH.¹¹

Beraprost is the first chemically stable and orally active prostacyclin analogue. Beraprost has demonstrated improvement in exercise capacity that persists for up to 3–6 months. However, there were no haemodynamic improvements or long-term outcome benefits.^{1,21}

Selexipag is a non-prostanoid oral drug that binds to and activates prostacyclin IP receptors in the pulmonary vasculature, but is not a prostacyclin derivative. Vascular endothelial cells secrete Endothelin-1 (ET-1) that causes vasoconstriction and proliferation of vascular smooth muscular cells. Thus, selexipag promotes pulmonary vasodilation, inhibits platelet aggregation, and has antiproliferative effects on pulmonary artery smooth muscle cells.^{3,19}

Endothelin receptor antagonists (ERAs) target both ET_A and ET_B receptors non-selectively (bosentan) or ET_A receptors selectively (ambrisentan and macitentan). Due to selectivity, stimulation of ET_A receptors causes vasoconstriction, whereas stimulation of ET_B receptors causes vasodilation. ERAs inhibit ET-1, which is elevated in PAH, from binding to its receptors, thereby preventing vasoconstriction and cellular proliferation.¹ They promote changes in lymphocyte maturation and the capacity of dendritic cells to present antigens to lymphocytes.¹⁹

Bosentan, a nonselective ET-1 receptor antagonist, reduces inflammation by decreasing intercellular adhesion molecules (ICAM)-1 and IL-6 levels in blood, which are correlated with stability of the hemodynamic condition.¹¹ Another study reports that bosentan inhibits ET-1 induced IFN-gamma release from CD4⁺ cells or endotoxin-stimulated cytokine release from pulmonary arterial smooth muscle cells.⁴ Thus, bosentan can modulate immune responses and reduce pulmonary vascular inflammation.^{1,4}

Nitric oxide (NO) is a powerful vasodilator synthesized from L-arginine by endothelial NO synthase (eNOS). NO activates soluble guanylate cyclase (sGC) causing an increment in intracellular cGMP, which like cAMP, stimulates the vasodilator and antiproliferative effects on pulmonary vascular smooth muscle.¹⁹ The natriuretic peptides increase cGMP in the pulmonary circulation by binding to the cell surface receptor linked to membrane-bound guanylyl cyclase.

Deficiencies in cGMP generation due to disordered NO and natriuretic peptide signaling have also been involved in the PAH pathogenesis.²⁴

Phosphodiesterase type 5 (PDE5) is the central enzyme responsible for cGMP degradation in pulmonary vascular smooth muscle, and its expression is increased in patients with PAH. Phosphodiesterase type 5 inhibitors (PDE5i), as sildenafil and tadalafil, retard the cGMP metabolism and stimulate the vasodilatory effects of NO and natriuretic peptides.¹⁹

Sildenafil, an PDE5i, inhibits the degradation of cGMP by competing with cGMP for the PDE5 binding site. cGMP activates protein kinases and a common regulator of ion channel conductance, glycogenolysis, and cell apoptosis.^{1,9,19} PDE5i has an immunomodulatory effect and influences angiogenesis by increasing the expression of vascular endothelial growth factor (VEGF), stimulate platelet activation, proliferation of regulatory T cells and production of pro-inflammatory cytokines and autoantibodies.²⁵ Although the immunomodulatory effects of PDE5 inhibitors seem promising, they have not yet been tested in clinical trials. Data on the influence of selective PDE5-Is on the potential immunomodulatory effects in humans remain to be confirmed.¹¹

While PDE-5 increases the NO/cGMP pathway, delaying cGMP degradation, the soluble guanylate cyclase stimulator (Riociguat) targets the NO pathway by stimulating soluble guanylate cyclase (sGC), and it is independent of endogenous NO.^{21,26} sGC is an enzyme in the cardiopulmonary system and the NO receptor. sGC simulators or sGC activators are drugs that increase the activity of sGC. They also cause vasodilation and smooth muscle relaxation by raising cGMP levels. PAH is associated with endothelial dysfunction, abnormal NO synthesis, and impaired stimulation of the NO-sGC-cGMP pathway.²⁶

Riociguat enhances the concentration of cGMP in vascular smooth muscle cell (VSMC) that activates the cGMP-dependent protein kinase (PKG), which leads to VSMC relaxation and vasodilation. Moreover, Riociguat has shown antifibrotic, anti-inflammatory and antiproliferative properties in experimental models, essential to controlling progression and treatment of PAH.^{1,26}

Different therapeutic responses among patients are observed due to the multifactorial pathogenesis of PAH, individual severity and susceptibility, disease evolution time and drugs with different mechanisms of action. In case of poor clinical response to initial monotherapy or combination, sequential dual or triple combination is recommended by ESC/ERS.^{1,21}

Novel Drug Therapies Targeting Specific Pathways in PAH

Traditional treatment strategies have focused on vasodilation of partially occluded vessels; however, this mechanism has not resulted in a sufficiently effective strategy to reverse or prevent disease progression. Therefore, there is a need for targeting surrogate pulmonary vascular remodeling and inflammatory pathways. Hence, current studies on human and animal models have gradually advanced understanding of the pathophysiology of PH, focusing on the inflammatory cascade process and vascular remodeling.^{1,27}

Experimentally, the exposure of animals to immunogenic stimuli, such as HIV, schistosomiasis, ovalbumin, overexpression of interleukin (IL)-6 and overexpression of Fra-2 can trigger PAH. Furthermore, in these models, blocking the inflammatory trigger prevented the pulmonary vascular disease phenotype (eg, schistosomiasis).²⁸ In experimental models of PAH, immunosuppressive drugs such as dexamethasone, mycophenolate mofetil, cyclosporine, tacrolimus and etanercept have demonstrated beneficial effects.²⁹ However, to date, none of the immune modulatory approaches have been tested in PH other than in connective tissue disease-associated PAH.¹

Circulating antinuclear antibodies, immunoglobulin and complement molecules have been identified in the pulmonary vascular endothelium of SLE-associated PAH. Rituximab (anti-CD 20), a monoclonal antibody that depletes B cells from the circulation, induces a targeted depletion of cellular lines expressing the CD20 antigen. This finding is frequently associated with a reduction in circulating autoantibodies characteristic of SLE.¹¹ In a recent pioneering randomized study, it was observed that B-cell depletion therapy with Rituximab may be a potential adjunct therapy to improve exercise tolerance and with acceptable safety for patients with systemic sclerosis-PAH.³⁰

Anakinra is a recombinant IL-1 receptor antagonist that works by blocking activity of interleukin. It is used to treat rheumatoid arthritis. In an open-label study of PAH after 14 days of treatment, high-sensitivity C-reactive protein and

symptom burden were significantly reduced.³¹ However, further research is needed to determine its efficacy and safety in PAH.

Due to the role of the BMPR2 pathway in maintaining endothelial integrity in pulmonary arteries, mutations that reduce signaling in this pathway promote endothelial dysfunction, increased cell proliferation, and accelerate pulmonary vascular remodeling.^{1,16}

Sotatercept is a selective ligand trap for transforming growth factor-beta (TGF- β) superfamily members such as activins and growth differentiation factors that can improve BMPR2 signaling and reduce pulmonary vascular smooth muscle proliferation and remodeling. In patients with background therapy, sotatercept resulted in a reduction in pulmonary vascular resistance in PAH.³²

Conclusion

Inflammation plays a key role in the pathophysiology of pulmonary hypertension. Recognition of the importance of inflammation as a powerful pathological driver of PAH open new perspectives for a more targeted treatment. Due to poor pulmonary arterial hypertension outcomes, despite treatments developed in recent decades, there is an urgent need for new drugs targeting new pathophysiological pathways. In experimental models of PAH, targeting inflammation by current or new immunosuppressive agents has delivered promising results in PAH inflammation and pulmonary vascular remodeling. Nevertheless, translating these findings to PAH in humans is necessary to assess the beneficial effects and safety of new drugs.

Disclosure

The authors report no conflicts of interest in this work.

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