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Contemporary Advances in Therapeutic Management of Pulmonary Hypertension

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Abstract **Review Article**

Pulmonary hypertension (PH) is a complex, chronic and a challenging condition that can be associated with several cardiac, pulmonary, and systemic diseases contributing to morbidity and mortality. Treating PH is multifaceted and concentrates on treatment of the underlying disorder, with referral to expert PH centres for individual assessment and tailored therapy. Targeted pharmacological and surgical treatments are available for patients with PH, for whom early referral to a specialist PH centre is recommended. Recent advancements in PH-targeted therapies and interventional-surgical procedures have contributed to the improvement in quality of life and survival in PH. This article gives an update on recent developments in the management of PH.

Keywords: Pulmonary Hypertension, Management, Therapy Advances.

INTRODUCTION

Pulmonary hypertension (PH) is a substantial global health issue. It is a chronic and progressive disease that presents like many other lung diseases, often leading to a delay in diagnosis, and therefore a delay in optimal therapy. It is defined as an increase of mean pulmonary arterial pressure ≥25 mmHg at rest. There are 5 clinical subcategories of this condition as: pulmonary arterial hypertension (PAH), PH due to left-sided heart disease, PH due to chronic lung disease, chronic thromboembolic PH (CTEPH), and PH with an unclear and/or multifactorial mechanisms [1].

Pulmonary Hypertension: Epidemiological Aspects

Overall, PH affects approximately 1% of the global population, and over half of patients with heart failure may be affected. Cardiologists are therefore likely to encounter PH in their practice [1, 2].

Reported evidence suggests that the 5-year overall survival rate of patients with PAH is only 59%. However, data indicate that many patients with PAH and right ventricular failure will die within 2 to 3 years after diagnosis if left untreated. Accurate diagnosis and classification are key to the overall survival rate [3].

Management of Pulmonary Hypertension: Current evidence

Pulmonary hypertension is divided into five major categories. Those that are of particular clinical relevance are pulmonary arterial hypertension, chronic thromboembolic pulmonary hypertension, and pulmonary hypertension due to left heart and lung diseases.

Treating PH is complex and is best carried out at specialized centres and with multidisciplinary approach. Group one PH treatment can be considered a stepwise progression, and typically requires referral to a centre equipped to diagnosis, treat, and monitor PAH. Calcium channel blockers such as nifedipine, diltiazem, and amlodipine are useful in patients with a positive vasoreactivity test. For patients with a negative vasoreactivity test or who have an inadequate response to calcium channel blockers. Treatment is focused on decreasing pulmonary vascular resistance and PAP but is not curative.

Ten drugs from five different substance classes are now available for the treatment of PH and are often given in combination. The treatment strategy is determined by risk stratification based on the severity of disease, along with the clinical phenotype and possible

accompanying illnesses. The preferred treatment for chronic thromboembolic pulmonary hypertension is surgical pulmonary endarterectomy; inoperable patients are treated with drugs and endovascular interventions. PH due to left heart and lung diseases generally calls for specific treatment of pulmonary hypertension only if there is severe right-heart strain [2].

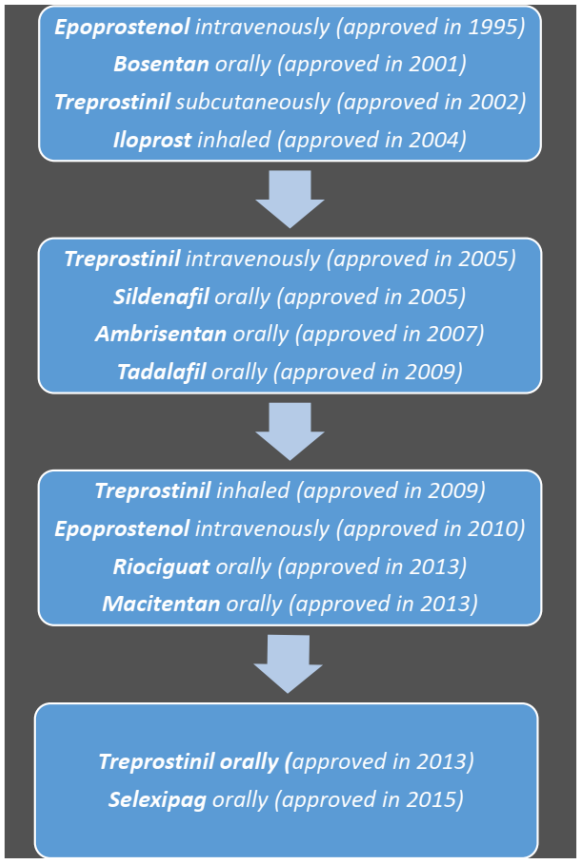

Figure: Journey of Drug Development for PH

Recommended dual combination therapies:

- Macitentan and sildenafil.
- Riociguat and bosentan.
- Selexipag and endothelin receptor antagonist or PDE-5i, or both.

Surgical pulmonary endarterectomy is the treatment of choice for eligible patients with CTEPH. Targeted treatments (phosphodiesterase type 5 inhibitors, soluble guanylate cyclase stimulators, endothelin receptor antagonists, prostacyclin analogues, and prostacyclin receptor agonists) are licensed for patients with PAH. The soluble guanylate cyclase stimulator riociguat is the only licensed targeted therapy for patients with inoperable or persistent/recurrent CTEPH. Management of PH resulting from left-sided heart disease primarily involves treatment of the underlying condition [1].

Endothelin receptor antagonists such as ambrisentan, bosentan, and macitentan bind to endothelin and inhibit vasoconstriction that is typically caused by endothelin. These can be given orally and are recommended for mild and moderate disease, NYHA class II and III. Phosphodiesterase 5 (PDE-5) inhibitors (tadalafil, sildenafil, vardenafil) inhibit enzymatic processes and result in increased cyclic guanosine monophosphate, causing pulmonary and systemic vasodilation. Prostaglandin analogs replete the decreased prostaglandin that is decreased in pulmonary hypertension. These activate the prostacyclin receptor which will ultimately lead to pulmonary vasodilation. Epoprostenol is given as a continuous intravenous infusion, and treprostinil may be given intravenously, subcutaneously, orally, and via inhalation. Patients with PH due to chronic thromboembolism should be referred for evaluation for endovascular thrombectomy. The final treatment option for patients who fail aggressive medical treatment is heart-lung transplantation [4].

Management of Pulmonary Hypertension: What is New?

New treatment options

Initial triple therapy vs. double may improve outcomes in newly diagnosed PAH, inhaled nitric oxide at higher dose shows beneficial role in Pulmonary Hypertension. New exploratory endpoint data from the INSPIRE study show improvements after 2 months of treatment with inhaled treprostinil in quality of life, 6-minute walk distance and New York Heart Association functional class.

Pathological mechanisms and potential therapeutic targets of PH

Various pathogenic factors, such as gene mutations, drugs/poisons, and hypoxia, can induce pulmonary arteriole vascular vasoconstriction, characterized by luminal stenosis, endothelial dysfunction, inflammation, infiltration, etc., ultimately causing RHF. The endothelin-1, prostacyclin, and nitric oxide pathways have been targeted in clinical practice and are three pivotal pathways approved in PAH management.

Current guidelines do not provide definitive recommendations regarding the place of selexipag in the treatment algorithm of PAH. Finally, the possibility of transition between the several drugs acting in the prostacyclin pathway, and the potential role of selexipag in chronic thromboembolic pulmonary hypertension and pediatric PAH is currently being examined, possibly expanding its future use. Use of oral add-on selexipag in children was well tolerated, safe and improved PAH outcomes, according to data published in The Journal of Heart and Lung Transplantation [6].

Inhaled treprostinil was well tolerated and significantly improved exercise capacity and other clinical outcomes over 16 weeks in patients with pulmonary hypertension associated with ILD, according to results of the INCREASE study [7]. Sotatercept Could Be a Promising Novel Agent for Pulmonary Arterial Hypertension: Sotatercept, a novel, first-in-class fusion protein therapy, significantly improved pulmonary-vascular, cardiovascular, and exercise-related outcomes in patients with pulmonary arterial hypertension (PAH) at 24 weeks, according to findings from the PULSAR trial. Sotatercept, binds activins and growth differentiation factors in the attempt to restore balance between growth-promoting and growth-inhibiting signaling pathways [8].

Pulmonary artery denervation has arisen as a novel intervention in the treatment of pulmonary arterial hypertension, and other forms of pulmonary hypertension, with the aim of reducing the sympathetic activity of the pulmonary circulation. Pre-clinical studies and initial clinical trials have demonstrated that the technique can be performed safely with some positive effects on clinical, haemodynamic and echocardiographic markers of disease [9].

PH in COVID era

As PAH patients have shown to have worse outcomes with all-cause hospitalizations, proactively working to decrease the risk of COVID-19 infection while continuing to provide a high-level of PAH care is essential.

Table: Drug options for Pulmonary Hypertension.

Class	New Drug	Mechanism of action
Drugs targeting genetic or epigenetic changes	**Chloroquine**	Prevents lysosomal degradation of BMPR2.
	Tacrolimus	activate BMP signalling
	Sotatercept	Recombinant activin receptor IIA (ActRIIA) ligand trap. Improves BMP/TGFbeta signalling.
	Etanercept	TNFalpha inhibitor. Antiinflammatory and prevents TNFalpha-mediated repression of BMPR2 synthesis
Drugs targeting inflammation	**Rituximab**	Depletes B cells.
	Tocilizumab	IL-6 receptor antagonist
	Anakinra	Recombinant IL-1 receptor antagonist.
Drugs targeting mitochondrial dysfunction and oxidative stress	**Bardoxolone methyl**	Orally active NF-kappaB inhibitor and Nrf2 inducer. Promotes synthesis of antioxidant molecules.
Drugs targeting metabolic and hormonal disturbances	**Human recombinant ACE2**	Catalytic synthesis of the protective RAS hormone angiotensin-(1-7).
	Tamoxifen	Oestrogen receptor modulator.
Drugs improving insulin resistance	**Metformin**	Promotes insulin sensitivity, endothelial NO synthesis and inhibits VSMC proliferation.
Drugs targeting proliferation	**Imatinib**	Tyrosine kinase inhibitor. Status: Five active trials. Improved 6MWD and reduced pulmonary vascular resistance in Phase III trial, but severe side effects (subdural hematoma) prevented approval.
	Seralutinib	Inhaled kinase inhibitor
New drugs for vasodilation	**Getagozumab**	Humanised, monoclonal, inhibitory endothelin ETA receptor antibody.
	Pemziviptadil:	Recombinant fusion protein with sustained release of vasoactive intestinal peptide for once/week s.c. application
	Zamicastat:	Dopamine β-hydroxylase inhibitor. Reduces sympathetic tone.

BMPR2=Bone morphogenetic protein receptor type II, ACE=Angiotensin converting enzyme.

CONCLUSION

Despite advances in therapies for PH, individualization of care is essential to choosing between various options. Sequential dual or tertiary therapy for patients with PAH who fail monotherapy is recommended by the ESC/ERS. Upfront dual or even tertiary therapy in selected patients with moderate-risk to high-risk features might be helpful in improving prognosis in these subsets of patients.

PAH remains a life-threatening disease with a poor diagnosis despite the emergence of several therapies. Potential therapeutic targets of PH are emerging with the growing understanding of pathological mechanisms. Therapeutic targets that focus on BMPR2 mutations, apoptosis of PAECs and proliferation of PASMCs, inflammation, epigenetic modifications, and metabolic pathways will attract increasing attention in the near future. However, potential therapies require further investigation before implementation. Different treatment approaches may potentially improve overall survival depending upon the distinct pathogenesis of the disease. The trials in near future might offer new insight into therapeutic interventions in patients with PAH.

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