Treatment of pulmonary hypertension: bench to bedside

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Summary
Pulmonary arterial hypertension is an orphan disease and a model for drug developments over recent years. Expert centers have focused basic science on the pulmonary vasculature and the right ventricle, followed by a direct transfer of innovative concepts to clinical research. Successful examples for translational experimentation are the endothelin receptor antagonists, prostacyclin receptor agonists, and the activators of soluble guanylate cyclase. On the other hand, there have been failures such as vasoactive intestinal peptide, statins, and escitalopram. Several new drugs and gene therapy are under investigation, thus significant advances are anticipated.

Introduction
Pulmonary hypertension is a hemodynamic and pathophysiological state that can be found in multiple clinical conditions, and is defined by an increase in invasively measured mean pulmonary arterial pressure \( \geq 25 \text{ mmHg} \) at rest.\(^1\) Untreated chronic pulmonary arterial hypertension leads to RV failure and death within 3 years of diagnosis.\(^2\) Recently, an updated classification and recommendations for contemporary diagnosis and treatment of PH have been issued as part of the new ERS/ESC guidelines.\(^1\) Incidences of PH are expected as low as 2.5 cases per million for pulmonary arterial hypertension (PAH), and as high as 60–70% of the population with systolic and diastolic left ventricular dysfunction.

This short update will only focus on group 1 pulmonary hypertension (i.e. PAH), including idiopathic, heritable, drugs and toxins induced, PAH associated with specific disease (connective tissue disease, HIV, portal hypertension, congenital heart disease, schistosomiasis, chronic haemolytic anaemia), and persistent pulmonary hypertension of the newborn. For this group most of treatment evidence is available and applicable. We will also review drugs in development, and drugs currently under clinical investigation (Table 1).

Pathophysiology
PAH may be classified as a disorder of pathological vasoconstriction. Increased vascular tone in PAH has been ascribed to endothelial cell dysfunction,\(^3\) which is characterized by a reduced expression of pulmonary vasodilators and increased expression of vasoconstrictors.\(^4\) Alternatively, PAH has recently been understood as the sequela of a disordered vascular remodeling process in response to an unknown injury where thrombotic and inflammatory processes, as well as deregulated repair by a deficiency in proteins of the TGF-beta-family are prominent. It is possible that both pathophysiological concepts are correct, and occurring in sequence. The result is a loss of functional pulmonary vessels. Patients with a hemodynamic responder status who later in their disease process develop severe pulmonary hypertension appear
Table 1
Treatment of pulmonary arterial hypertension

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<th>Class of drug</th>
<th>Guideline recommendation</th>
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<td>WHO-FC II</td>
<td>WHO-FC III</td>
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<td>Endothelin receptor antagonists</td>
<td>Ambrisentan, Bosentan</td>
<td>Ambrisentan, Bosentan</td>
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<td>PDE-5 inhibitors</td>
<td>Sildenafil, Tadalafil</td>
<td>Sildenafil, Tadalafil</td>
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<td>Activators of soluble guanylate cyclase</td>
<td>Epoprostenol, Iloprost, Treprostinil, Beroprost</td>
<td>Epoprostenol, Iloprost, Treprostinil</td>
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<td>Prostacyclin analogues</td>
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<td>Prostacyclin receptor agonists</td>
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<td>Sex hormones</td>
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<td>RAAS</td>
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<td>Beta-blockers</td>
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<td>Rho-kinase Inhibitors</td>
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PDE: phosphodiesterase; RAAS: renin-angiotensin-aldosterone system; KMUP-1: xanthine derivate 7-[2-[4-(2-chlorophenyl)piperazinyl]-ethyl]-1,3-dimethylxanthine; NOS: nitrate oxide synthase.

to be clinical examples matching this pathophysiologic concept.

Based on the mechanism of vascular loss, and the successes of organ transplantation restoring right ventricular function by introducing an allogeneic pulmonary vascular bed, recent scientific efforts have been directed at regrowing the pulmonary vascular bed with autologous transformed or inducible stem cells.

**Targeted treatments - vasodilators**

Initially, alpha- and beta-adrenergic blockers were employed without favorable results. A new era in managing patients with pulmonary hypertension began in the late 1970s with prostacyclins that produced significant pulmonary vasodilator activity. Higenbottam was the first to employ intravenous prostacyclin in patients in 1984. Later, new drugs targeting endothelial dysfunction such as endothelin receptor antagonists and phosphodiesterase-5 (PDE-5) inhibitors were developed.

Prostacyclin is a member of the endogenous prostanoids family and is synthesized from arachidonic acid. This is a multistep process, which involves prostacyclin synthase and cyclooxygenase. Prostacyclin is released by endothelial cells in the pulmonary circulation and its effects are mediated by a specific cell-surface receptor, which belongs to the G-protein coupled receptor class. The receptor has been located on platelets and endothelial cells. Upon binding of prostacyclin the receptor activates protein kinase A, leading to inhibition of platelet aggregation, relaxation of smooth muscle and vasodilation of the pulmonary arteries, which makes prostacyclins and its analogues powerful drugs in pulmonary hypertension. Synthetic prostacyclin analogues epoprostenol, iloprost and treprostinil are in clinical use. These drugs have improved exercise tolerance, Borg Dyspnea scores, hemodynamics, and survival. This benefit comes at a cost of some side effects, particularly during epoprostenol therapy. This specific agent has the disadvantage of requiring a permanent intravenous catheter and an infusion pump, which may lead to serious complications such as thrombosis, infection and shock. Endothelins comprise a family of 21 amino-acid peptides that play a key role in the regulation of vascular tone. ET-A and ET-B receptors bind the endothelin peptides, mainly endothelin-1. While the ET-A receptor is predominantly expressed on pulmonary smooth muscle cells, the ET-B receptor is located on both pulmonary vascular endothelial cells and smooth muscle cells. Activation of the ET-A receptor leads to potent vasoconstriction that persists after endothelin-1 is dissociated from the receptor, which is mediated via calcium. Moreover endothelin-1 has been described as a potent mitogenic factor for vascular smooth muscle cells. Currently, there are two commercial endothelin receptor antagonists approved for pulmonary arterial hypertension, bosentan and ambrisentan, which inhibit both vasoconstriction and smooth muscle cell proliferation, thereby improving quality of life and survival. Phosphodiesterase-5 inhibitors like sildenafil enhance the downstream effects of NO mediated vasodilation by increasing intracellular cGMP. NO has profound anti-
proliferative effects.18 The levels of cGMP are regulated by phosphodiesterases (PDE). To date, 11 different families of PDE isoenzymes have been identified. PDE-5 is the main pulmonary PDE target because it is highly expressed in the lungs. At the same time, its expression is low in the systemic circulation.19 The expression of PDE-5 is enhanced in pulmonary hypertension, resulting in increased metabolism of cGMP.20 In addition to sildenafil, tadalafil is approved by the FDA.21,22

The first oral selective prostacyclin-receptor Agonist Selexipag was safe and efficacious in a 17-week proof-of-concept trial with a PVR reduction of 30%. Another recent development is the class of activators of soluble guanylate cyclase (Prototype Riociguat) that has been tested and found efficacious in another proof-of-concept trial.

Targeted treatments - introducing reverse remodeling

Tyrosine kinase inhibitors (Prototype Imatinib)

Imatinib, a PDGF receptor blocker did not improve 6MWD in a first proof-of-concept trial but reduced PVR by 300 dyn·sec·cm⁻⁵, and increased cardiac output, particularly in patients with severe hemodynamic compromise. Further compounds in clinical trials are multikinase inhibitors, e.g. sunitinib.

Targets of new preclinical developments

Beta estradiol

Beta-estradiol has been a substance of interest because of the protective effect of female gender in pulmonary vascular disease.23 Its protective effects are mediated by a reduction of endothelin-1 expression, enhancing NO- and prostacyclin-synthesis and downregulation of various adhesion molecules.24 Furthermore, estrogen has antiproliferative properties.25 Recently, Xu et al. have shown that beta-estradiol treatment of rats with pulmonary hypertension led to a reduced degradation of p27(kip1) by reduction of Skp-2 expression. p27(kip1) is a negative regulator of pulmonary artery smooth muscle cell growth26 thus reversing vascular remodeling. However, 17beta-estradiol may induce pulmonary hypertension by inducing proliferation, which is dependent on an interaction with serotonin and the 5HT₁b receptor.27 Clearly, the role of beta-estradiol in pulmonary hypertension merits further studies.

Renin-angiotensin-aldosterone system (RAAS)

Angiotensin-converting enzyme 2 (ACE-2) is a homologue of ACE and represents the counter regulatory axis of ACE, reducing the vasoconstrictive proliferative, fibrotic and inflammatory effects of angiotensin-2.28 ACE-2 has mechanistically been implicated in several pulmonary diseases including acute respiratory distress syndrome,29 where a knock-out of ACE-2 led to more severe disease.30 There is a wealth of animal data suggesting that the use of an ACE-inhibitor or a AT1 receptor antagonist attenuates development of pulmonary hypertension. Data from human pilot studies are controversial. While cilazapril reduced mean pulmonary pressure in patients with congestive heart failure and captopril reduced pulmonary pressure in patients with high-altitude pulmonary hypertension, enalapril had no effect.30 The observation that RAS exerts an effect on the pulmonary vasculature makes the endogenous counterpart of ACE - ACE-2 - an interesting target for future drug development.

RhoA/Rho-kinase

Rho A and its downstream effector Rho-kinase play an important role in the development of cardiovascular diseases including pulmonary hypertension. Rho-kinase mediates a calcium-sensitization in vascular smooth muscle cells, thereby elevating vascular tone and its inhibitor has been shown to act as a vasodilator in pre-constricted arteries.31 Recently, a xanthine derivate called KMUP-1 has been shown to increase NO synthesis and inhibit RhoA/Rho-kinase in a rat model of pulmonary hypertension.32 KMUP-1, a xanthine-based cyclic GMP-enhancing Rho-kinase inhibitor increased the expression of eNOS, soluble guanylate cyclase and cGMP, while decreasing PDE-5 and Rho-kinase expression, leading to calcium desensitization in pulmonary vascular smooth muscle cells.

Gene therapy

Bull et al. found 106 genes differentially expressed in PAH lungs, including bone morphogenic protein receptor II (BMPR-II), vasoactive intestinal peptide and several chemokine receptors.33 This observation gave rise to the idea to correct altered gene expression via gene transfer, carrying the theoretical advantage that there are no systemic side effects of vasodilatation.34 Several genes have been targets of gene therapy in preclinical studies including eNOS,35 vascular endothelial growth factor,36 calcitonin-gene-related peptide,37 adrenomedullin,38 prostacyclin synthase39 and BMPR-II.40 All of these improved pulmonary hemodynamics in animal models. At this stage of gene therapy, benchwork and clinical work run in parallel, with the expectation of significant advances still to come.

Conclusions and clinical implications

Both basic and clinical research have been contributing to innovative drug developments for PAH, thus improving quality of life, survival and freedom of hospitalizations in this orphan disease population.41 Nevertheless, prognosis of PAH is still dismal, and as clinical studies become more demanding in an ageing and more comorbid European population, visionary individuals who are networking in an environment of decreasing resources drive scientific advances.

Conflict of interest statement

Irene M. Lang entertains the following relationships with commercial interests related to this presentation existed during the past 12 months: research grants, consultancies, advisory Board, or lecture fees: Actelion, Bayer Schering, Gilead, Novartis, Pfizer, United Therapeutics, AOP-Orphan.

References


