LEARNING THE ROPES: PULMONARY HYPERTENSION

Actual and novel treatments for pulmonary hypertension

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The current management of pulmonary arterial hypertension (PAH) consists of a **combination of pharmacological and non-pharmacological measures**. In contrast to the treatment of systemic arterial hypertension, treatment success is quite limited as PAH is a progressive, incurable disease which is extremely difficult to approach therapeutically. Thus, treatment goals are, among others, usually defined as a 6-minute walking distance (6MWD) of >380 to >500 m with >440 m currently accepted as standard by the most recent ESC/ERS guidelines of 2016¹. Here, only general therapeutic strategies are dealt with. For special cases of PAH such as PAH in children, congenital heart disease, connective tissue disease, portal hypertension or HIV please refer to respective guidelines^{1,2}.

Current Drug treatment of PAH follows the “traditional” concepts of PAH pathophysiology. According to these, the disease process is governed by an imbalance of endogenous vasoactive agents in lung vessels: increased activity of endothelial vasoconstrictors such as endothelin and thromboxane, reduced activity of vasodilators such as nitric oxide (NO) and prostacyclin. Current treatment strategies aim to restore the balance at least to a certain extent.

According to the ESC/ERS guidelines¹ (a new edition is underway but not yet published), **the treatment strategy** can be divided in three steps:

1) General measures including physical activity, psychosocial support, supportive therapy (oral anticoagulants, diuretics, O₂, digoxin), referral to an expert center and acute vasoreactivity testing

for the indication of chronic therapy with calcium channel blockers (CCB).

2) Initial therapy with high-dose CCB in vasoreactive patients or with drugs approved for PAH in non-vasoreactive patients.

3) If the response to initial therapies is insufficient, combination of approved drugs and lung transplantation follow, if drug treatment is unsuccessful.

Approval of **drugs for the treatment of PAH** is based on their effects in evidence-generating studies in patients with different forms of PAH^{1,2}. Due to the specific characteristics of lung vessels featuring some vasodynamic deviations from the systemic circulation, these drugs are lung-specific and not in use for the treatment of systemic arterial hypertension.

Drug monotherapy can be begun with members of the following drug classes:

- **Endothelin receptor antagonists** to block the actions of the vasoconstrictor endothelin: *Ambrisentan, Bosentan, Macitentan*,

- **Phosphodiesterase type 5 inhibitors** to block the degradation of the cyclic Guanosine-Monophosphate (cGMP) which generates the vasodilator NO: *Sildenafil, Tadalafil, Vardenafil*,

- **Guanylate cyclase “stimulators”** activating the enzyme soluble Guanylate cyclase (sGC) to generate cGMP which in turn induces vasodilation via further signaling steps: *Riociguat*,

- **Prostacyclin analogues** which replace/mimic the vasodilator prostacyclin: *Epoprostenol*, *Iloprost*, *Treprostinil*, *Beraprost*. These drugs cannot be applied orally with the exception of *Treprostinil* and *Beraprost* (used mainly in Asia),

- **IP receptor agonists** to selectively stimulate the prostacyclin (IP) receptor leading to vasodilation: *Selexipag* (oral).

Similar to the drug treatment of systemic arterial hypertension, **initial combination therapy** has gained increasing attention as an attractive option to simultaneously address the different pathophysiological pathways of PAH. Recommended combinations include:

- Endothelin receptor antagonist (ERA) *Ambrisentan* + Phosphodiesterase 5 inhibitor (PDE-5i) *Tadalafil* ³,

- *Bosentan* (ERA) + *Sildenafil* (PDE-5i) + *Epoprostenol* i.v. (Prostacyclin analogue)⁴,

- *Bosentan* + *Epoprostenol* i.v.⁵,

- ERA or PDE-5i + other i.v. prostacyclin analogue.

An alternative to initial combination therapy is **sequential combination therapy**. Evidence has been generated for numerous dual and triple combinations between the different drug classes^{1,2} with the exception of the combination of the CGMP stimulator *Riociguat* with PDE-5i (hypotension, safety issues)⁶.

New and more efficient drugs for PAH remain a major unmet medical need. A better understanding of pathomechanisms leading to vascular remodelling and to the cancer-like phenotype of pulmonary vascular cells is the basis for many new drug targets^{7,8}.

A search on www.clinicaltrials.gov on January 24th, 2021, for clinical trials in PAH revealed 103 Phase I, II or III trials within the last 5 years, which are either “completed”, “recruiting”, “not yet recruiting” or “active, but not recruiting”.

The following provides an overview about drugs targeting novel targets in PAH and their current status in clinical/preclinical drug development for PAH.

Drugs targeting genetic or epigenetic changes:

The best characterized genetic defect in PAH are mutations leading to an impairment of bone

morphogenetic protein receptor type II (BMPR2) signalling thus promoting vascular remodelling. The following drugs target impaired BMPR2 signalling.

- **Gene therapy:** Adenoviral BMPR2 gene delivery. **Status:** Preclinical.

- **Chloroquine:** Prevents lysosomal degradation of BMPR2. **Status:** Preclinical.

- **Tacrolimus (FK506):** Identified by high-throughput screening of 3.756 FDA-approved drugs to activate BMP signalling. **Status:** Improved 6-min walk distance (6MWD) and increased BMPR2 expression in a Phase II trial, but only in a subgroup of patients. No Phase III study initiated.

- **Sotatercept:** Recombinant activin receptor IIA (ActRIIA) ligand trap. Improves BMP/TGFβ signalling. **Status:** Successfully tested in Phase II trial. Ongoing Phase III study.

- **Etanercept:** TNFα inhibitor. Anti-inflammatory and prevents TNFα-mediated repression of BMPR2 synthesis. **Status:** Preclinical.

Drugs targeting reversible, epigenetic abnormalities are thought to prevent the hyperproliferative phenotype, inflammation and fibrosis in PAH.

- **HDAC-inhibitors.** **Status:** Preclinical.

- **Apabetalone:** Inhibits epigenetic mechanisms involving bromodomain and extra-terminal motif (BET) proteins. **Status:** Ongoing Phase Ib trial.

Drugs targeting inflammation:

Pulmonary perivascular inflammation is a hallmark of PAH. There have been many attempts to repurpose anti-inflammatory drugs.

- **Rituximab:** Depletes B cells. **Status:** Significantly improved 6MWD after 24 weeks of treatment in a Phase II trial in PAH associated with systemic sclerosis, but this effect was lost by week 48. Currently not continued.

- **Tocilizumab:** IL-6 receptor antagonist. **Status:** Unsuccessful Phase II “TRANSFORM-UK” trial.

- **Anakinra:** Recombinant IL-1 receptor antagonist. **Status:** Pilot study showed improvement of CRP levels, heart failure, IL-6 levels and quality of life. Phase III trial expected.

Drugs targeting mitochondrial dysfunction and oxidative stress:

Oxidative stress/reactive oxygen species are increased in PAH. They are caused by and trigger inflammation, which makes them an interesting drug target.

- **Bardoxolone methyl:** Orally active NF-kappaB inhibitor and Nrf2 inducer. Promotes synthesis of antioxidant molecules. **Status:** Successful Phase II trial with significant increase in 6MWD (LARIAT). Phase III trial (CATALYST) initiated, but terminated early because of COVID-19 pandemic.

Drugs targeting metabolic and hormonal disturbances:

The renin-angiotensin system (RAS) is overactivated in PAH, but conventional RAS blockade is ineffective. New drugs target the protective arm of the RAS.

- **Human recombinant ACE2** (*hrACE2*; GSK2586881; *APN01*): Catalytic synthesis of the protective RAS hormone angiotensin-(1-7). **Status:** Completed pilot and Phase II studies showing improvement of pulmonary hemodynamics. Development of GSK2586881 for PAH has discontinued for strategic reasons.

- **C21:** Angiotensin AT2-receptor agonist. **Status:** Ongoing Phase II trial in idiopathic pulmonary fibrosis.

A role of oestrogens in PAH has been suspected because of higher prevalence in women and increased oestrogen levels in males with PAH.

- **Tamoxifen:** Oestrogen receptor modulator. **Status:** Ongoing Phase II trials.

- **Anastrozole:** Aromatase inhibitor preventing formation of oestrogens from androgens. **Status:** Ongoing Phase II trials.

Drugs improving insulin resistance are tested, because insulin resistance is a risk factor for PAH.

- **Metformin:** Promotes insulin sensitivity, endothelial NO synthesis and inhibits VSMC proliferation. **Status:** Three ongoing Phase Ib/II trials.

Drugs targeting proliferation:

Targeting proliferation in PAH mainly aims at reducing vascular remodelling. Several anti-cancer drugs are tested for repurposing.

- **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. **Status:** Ongoing Phase Ib trial.

- **Elafin:** Endogenous elastase inhibitor and tumour suppressor. **Status:** Phase I trial.

- **Olaparib:** PARP inhibitor. Promotes cell death by preventing DNA repair. **Status:** Phase Ib trial.

New drugs for vasodilation:

- **Getagozumab (GMA301):** Humanised, monoclonal, inhibitory endothelin ET_A receptor antibody. **Status:** Ongoing Phase Ib trial.

- **Pemziviptadil:** Recombinant fusion protein with sustained release of vasoactive intestinal peptide for once/week s.c. application. **Status:** Ongoing Phase II trial.

- **Zamicastat:** Dopamine β-hydroxylase inhibitor. Reduces sympathetic tone. **Status:** Ongoing Phase II trial.

Future will tell whether one or more of these novel treatment approaches will become a breakthrough in PAH drug treatment which is desperately hoped for in view of the currently limited therapeutic perspectives.

In summary:

The management of PAH, a difficult-to-treat condition, consists of drug- and non-drug strategies. Referral to an expert center is crucial whenever possible. Following general measures like physical activity, oral coagulants, diuretics, or O₂ administration, specific drug treatment follows conventional concepts about PAH pathophysiology trying to restore the disturbed balance between vasoconstrictor and vasodilating principles in pulmonary arteries. Due to specific features of the lung circulation, PAH drugs differ from those used in systemic arterial hypertension. High dose calcium channel blockers (CCB) are first-line in vasoreactive patients. Non-vasoreactive

patients receive either monotherapy or, more frequently, combined drug treatment right from the beginning or in sequential order. Drugs used are endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, guanylate cyclase stimulators, prostacyclin analogues, and IP (prostacyclin) receptor agonists. The search for novel, more potent, drugs has revealed new

targets including genetic or epigenetic changes, inflammation, mitochondrial dysfunction and oxidative stress, metabolic and hormonal disturbances, proliferation, and vasodilation. More than one-hundred clinical trials are underway with these new approaches, and a breakthrough with one or more of these is eagerly awaited.

Figure 1: Treatment algorithm in PAH Modified from 1) with permission

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