



Pulmonary hypertension: modern methods of treatment and ways of their long-term development

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Abstract

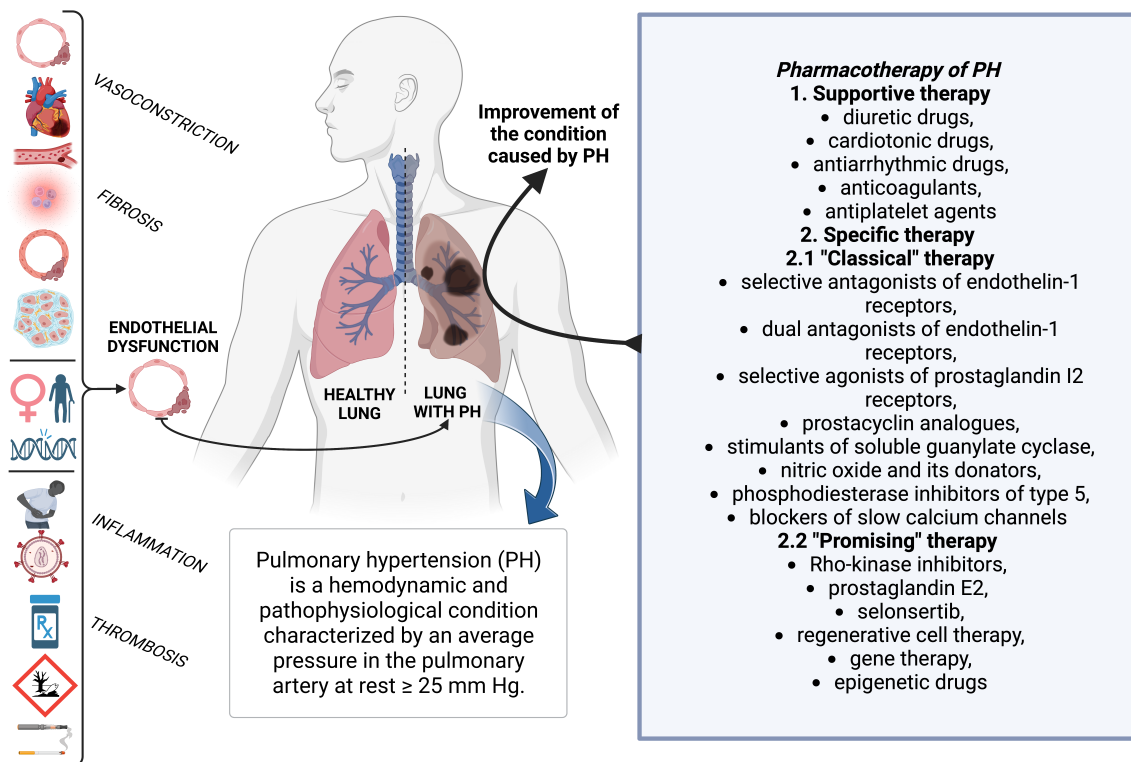
Introduction: The purpose of this work is to review the main pathogenetic mechanisms of the development of pulmonary hypertension (PH), as well as modern established methods of treatment of PH and to consider new most relevant and promising possibilities of therapy for this pathology.

Materials and Methods: Electronic resources were used as the main sources of information for this work. Research papers that were predominantly selected included reports of clinical and preclinical trials, clinical guidelines, data from various registries, systematic reviews, and meta-analyses. All received data were analyzed and structured.

Results and Discussion: In the modern structure of diseases, pulmonary hypertension has a significant place, affecting about 1% of the population. However, each of its main groups has its own characteristics. At the same time, despite the multiplicity of etiological factors, the main pathogenetic link in the development of pulmonary hypertension is endothelial dysfunction. After that, the main established approaches to the treatment of pulmonary hypertension are the following: general recommendations for patients, drugs used as supportive nonspecific therapy, as well as specific conservative and radical methods of treatment. In addition, the main modern directions of scientific research in the field of treatment of pulmonary hypertension are described: stem cells, gene therapy and epigenetic drugs.

Conclusion: Despite active research and many different drugs intended for the treatment of pulmonary hypertension, this pathological condition remains an urgent health problem. Thus, the search for new points of application of therapy and fundamentally new methods of treatment of pulmonary hypertension remains relevant to this day.

Graphical abstract:



Keywords

pulmonary hypertension, endothelial dysfunction, treatment methods

Introduction

Pulmonary hypertension (PH) has never lost its relevance in the global healthcare environment since its discovery at the end of the IX century. On the contrary, more and more new works and studies reveal the connection of PH with various pathological conditions of the cardiovascular and respiratory systems, as well as many infectious and hereditary diseases (Galiè et al. 2016; Rosenkranz et al. 2016; Olschewski et al. 2018). This is suggested by the fact that over the past 20 years the number of publications on this topic has increased by more than 5 times (Fig. 1).

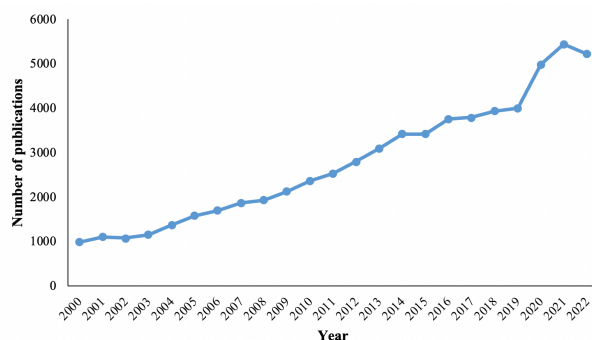


Figure 1. The number of scientific papers on the topic of pulmonary hypertension on the PubMed Internet resource in the period from 2000 to 2022.

The purpose of this work is to review the main pathogenetic mechanisms of the development of PH, as well as modern established methods of treatment of various types of PH and to consider new most relevant and promising possibilities of therapy for this pathology.

Materials and Methods

Electronic resources, such as PubMed, were used as the main sources of information for this work. Research papers that were predominantly selected included reports of clinical and preclinical trials, clinical guidelines, data from various registries, systematic reviews, and meta-analyses. In this case, information from works published no earlier than 2013 was mainly used. However, it is worth noting that in this work there are references to earlier publications, if their information is fundamental and extremely important. Naturally, the main keyword used to search was "pulmonary hypertension". All the data obtained were analyzed and structured.

Results and Discussion

Definition. Epidemiology

PH is a hemodynamic and pathophysiological condition characterized by mean resting pulmonary artery pressure

pressure (RPA) ≥ 25 mm Hg. Etiopathogenetically, PH is divided into 5 main groups: 1) arterial pulmonary hypertension (PAH) and pulmonary veno-occlusive disease; 2) PH which develops due to diseases of the left heart; 3) PH which develops due to diseases of the respiratory system; 4) Chronic thromboembolic pulmonary hypertension (CTEPH); 5) PH with unclear and/or multifactorial mechanisms of development.

Pulmonary arterial hypertension is described as a subset of pathological conditions characterized hemodynamically by precapillary pulmonary hypertension with increased pulmonary vascular resistance (PVR), which is $PLA \geq 25$ mmHg at normal pulmonary artery wedge pressure (PAWP) ≤ 15 mm Hg, and $LSS > 240$ $\text{din} \times \text{s} \times \text{cm}^{-5}$ (Galiè et al. 2015, 2016).

However, for the diagnosis of pulmonary arterial hypertension, in addition to meeting these criteria, it is also necessary to exclude other forms of precapillary pulmonary hypertension. This is especially important in diseases of the lungs and left heart with normalized PAWP.

In the modern structure of diseases, PH has a significant place, affecting about 1% of the population. At the same time, in age-related patients (over 65 years old), the incidence rates increase to 10% (Hoeper et al. 2017). However, it is worth noting that the epidemiological indicators of various etiopathogenetic groups differ significantly.

Information on the prevalence and incidence of PAH is currently provided by various national and international registries. According to one of these registries, these rates were 15 and 2.4 cases per 1 million adults, respectively (Humbert et al. 2006). At the same time, in the structure of PAH, its idiopathic form (IPAH) invariably occupies the first place, ranging from 41% to 50%, according to various registries. A smaller proportion is occupied by cases of hereditary PAH (0.4%) associated with congenital heart defects (36%), systemic connective tissue diseases (19.5%), portal hypertension (1.9%), HIV infection (0.4%) and taking drugs and toxins (0.4%) (Benza et al. 2010; Chazova et al. 2019).

Speaking about IPAH, it is also worth noting that the female population is most often affected by this pathology (Badesch et al. 2010; Humbert et al. 2010). The ratio of women to men diagnosed with IPAH ranges from 1.7:1 to 2.3:1, according to various registries (Hoeper et al. 2013).

The most common form in the structure of PH is its form which develops in the pathology of the heart, accounting for from 48% to 80% of the total number of all registered cases of PH (Rosenkranz et al. 2018). PH is formed in many patients with systolic (60%) and diastolic (83%) left ventricular failure, as well as with defects of the mitral valve (with stenosis – in 38% of cases, with insufficiency – 23%) and aortic (29% and 16% with stenosis and insufficiency, respectively) of the valves.

In obstructive pulmonary diseases, PH has a rather heterogeneous prevalence. So, in idiopathic pulmonary fibrosis, PH is determined in 8-15% of patients at the initial stage, in the late stage – in 30-50% and in the final stage – in more than 60% (Raghu et al. 2015). While in chronic obstructive pulmonary disease stage IV, about 90% of patients have signs of PH at rest (Nathan et al. 2019).

Determining the epidemiological indicators of CTEPH is currently a rather difficult task. On the one hand, in itself, a reliable diagnosis of this condition causes certain difficulties. On the other hand, overdiagnosis of CTEPH is quite common in patients with acute pulmonary embolism, while CTEPH, reliably verified during transventional catheterization of the heart, is found on average in 3.4% of patients who have undergone pulmonary embolism (Simonneau et al. 2017).

Etiology and pathogenesis

PAH is a disease that affects the small pulmonary arteries. Proliferation of the intima and middle membrane, thickening of the adventitia with the formation of foci of perivascular inflammation in PAH are the result of a violation of the processes of apoptosis of endotheliocytes and/or angiogenesis, followed by obliteration of the pulmonary vessels (Humbert et al. 2019). Such disorders can be the result of both mutations in various genes (BMPR2, which controls cell proliferation; KCNK3, which is responsible for caveolin-1 and potassium channels, etc.), and epigenetic mechanisms (DNA methylation, histone modifications) (Olschewski et al. 2018). Moreover, the role of a number of drugs and toxins that may be risk factors for the development of PAH has been identified. Such substances include *aminorex*, *dasatinib*, *metformins*, *cocaine*, etc. (Galiè et al. 2016; Simonneau et al. 2019). Complete or partial vascular obstruction resulting from all of these mechanisms leads to a progressive increase in vascular resistance. This increases the right ventricular afterload of the heart and hence leads to right ventricular heart failure.

Despite the heterogeneity of various pathologies of the left heart, as a rule, the development of PH in these cases has the same general mechanism. Systolic and/or diastolic overload of the left ventricle leads to stretching of the left atrium and an increase in pressure in it. Passive transfer of elevated pressure from the left side of the heart to the venous vessels of the lungs leads to damage to the endothelium with a subsequent decrease in the synthesis of *nitric oxide* (NO) and a decrease in sensitivity to various vasodilators. These changes naturally increase PVR and lead to an increase in mean PAP (Rosenkranz et al. 2016).

The basis of PH in lung pathology is persistent hypoxemia with subsequent vasoconstriction in the pulmonary circulation system and further remodeling of arterial vessels. Rigidity of the pulmonary vessels and damage to their endothelial layer, in turn, leads to an increase in PVR and, as a result, an increase in pressure in the pulmonary artery system (Klinger et al. 2016).

Pathogenetic relationships in CTEPH are complex and currently not well understood. However, even now we can say that the development of this pathology is due not only to the fact of chronic obstruction by thrombotic masses. This is evidenced by the fact that severe hypertension observed in CTEPH can develop in conditions of damage to less than 50% of the arterial bed. On this basis, it can be concluded that in the pathogenesis of CTEPH, disorders of angiogenesis, fibrinolysis and other neurohumoral factors play a significant role (Simonneau et al. 2017).

Summing up, we can say that, despite the multiplicity of the initial causes of the development of PH, its most important link in the pathogenesis is endothelial dysfunction.

Vasoconstriction in this case is due to abnormal function or expression of potassium channels and endothelial dysfunction, which in turn leads to a decrease in the production of vasodilators such as NO and prostacyclin and an increase in the production of vasoconstrictors such as endothelin-1 (Soldatov et al. 2018; Shchelykin et al. 2022).

Treatment

Treatment of PAH, like any form of PH, can be roughly divided into three main components: general recommendations, maintenance therapy, and specific therapy.

The ESC/ERS Guidelines for the Diagnosis and Management of Pulmonary Hypertension report positive effects of physical activity within symptom limits in patients with PH (Galiè et al. 2015; Galiè et al. 2016). Studies have shown the beneficial effects of exercise on performance, quality of life and cardiac function in patients with PH (de Man et al. 2009; Chan et al. 2013; Ehlken et al. 2016; Grunig et al. 2021). However, it is necessary to focus on the fact that before embarking on a physical rehabilitation program, patients should be selected the optimal pharmacological therapy that ensures a stable clinical condition. (Grünig et al. 2019). In addition, special rehabilitation measures and active physiotherapy are equally helpful in improving physical performance, quality of life and cardiac function in patients with pulmonary hypertension. (Ehlken et al. 2016).

Separately, it should be noted that patients with PH should be strongly recommended regular vaccination against the influenza virus, Streptococcus pneumoniae and the SARS-CoV-2 virus, due to the high mortality rates of patients with PH from various types of pneumonia (Galiè et al. 2016).

Also, an important aspect of working with a patient is the development of adherence to therapy, since PAH therapy often involves taking a large number of drugs with many side effects.

Supportive therapy

As a non-specific therapy in the presence of signs of hypoxemia (with arterial $pO_2 < 60$ mm Hg), patients with PAH should be given oxygen therapy. Under the influence of oxygen, the degree of hypoxia decreases and, as a result, the vasoconstriction of the vessels of the pulmonary circulation also decreases. Ambulatory oxygenation should be considered if it results in a subjective improvement in the patient's condition (Ulrich et al. 2017, 2109). Nocturnal oxygen therapy should be considered in case of sleep-related hypoxia (Adir et al. 2021). However, there are no randomized clinical trials confirming the beneficial effect of long-term oxygen use. A significant contribution to hypoxemia is often made by concomitant lung pathology, the adequate treatment of which, in combination with oxygen therapy, favorably affects the course of PAH.

In patients with PAH, it is important to monitor iron levels. Iron deficiency is defined as serum ferritin < 100 $\mu\text{g/l}$ or serum ferritin 100-299 $\mu\text{g/l}$ in conjunction with transferrin saturation $< 20\%$ (McDonagh et al. 2018). In PAH patients, iron deficiency correlates with myocardial dysfunction, worsening of symptoms, and increased risk

of mortality (Van De Bruaen et al. 2011; Sonnweber et al. 2018).

Diuretics are indicated for patients with signs of overhydration. However, data on their effectiveness in PAH are extremely scarce. Loop diuretics are commonly used, often in combination with mineralocorticoid receptor antagonists. It is important to note that, in the case of the appointment of diuretics, patients should also be advised to regularly monitor body weight and consult a doctor in case of weight gain. In the management of patients with PAH, renal function and serum electrolytes should be regularly monitored, and a decrease in intravascular volume should be avoided, as this may cause a further decrease in systolic volume and systemic arterial pressure. Also, we should not forget that fluid retention and edema do not always signal right-sided heart failure, but can also be a side effect of PAH therapy (Stickel et al. 2019).

Data on the use of another group of nonspecific drugs - anticoagulants - are rather contradictory. The largest COMPERA registry analysis to date has shown a potential survival benefit associated with anticoagulants in patients with idiopathic PAH (Olsson et al. 2014), but this finding has not been confirmed by other studies (Preston et al. 2015). Two recent meta-analyses have also shown that the use of anticoagulants may improve survival in patients with idiopathic PAH (Khan et al. 2018; Wang et al. 2020); but they also did not have a reliable methodology. Data obtained from PAH registries (REVEAL, COMPERA) also did not give a clear answer about the effect of indirect anticoagulants on survival in patients with PAH; moreover, their use in patients with PAH was accompanied by an increased risk of mortality due to more frequent bleeding (Ngian et al. 2012; Olsson et al. 2014; Said, 2014; Preston et al. 2015; Roldan et al. 2017). Hypocoagulation is often recorded in patients with congenital heart defects and portopulmonary hypertension due to impaired synthesis/degradation of coagulation factors, as well as due to thrombocytopenia and thrombasthenia. In addition, in patients with cirrhosis of the liver, esophageal varices, hemorrhoidal veins can be the source of bleeding, and in patients with PAH on the background of congenital heart defects, dilated bronchial arteries. Thus, at present, anticoagulants are not recommended for general use in PAH. In general, the appointment of anticoagulants in patients with PAH can be considered only in the presence of documented arterial or venous thrombosis, atrial fibrillation/flutter, right ventricular heart failure (Galiè et al. 2016; Grünig et al. 2018; Goncharova et al. 2019).

Also, to date, there is no reliable evidence of the effectiveness of therapy with inhibitors of platelet aggregation in patients with PAH. Therefore, the routine administration of antiplatelet agents is not recommended as a pathogenetic one, but can be used if there are indications for the treatment of comorbidities.

In patients with PAH, supraventricular arrhythmias are often observed (Rajdev et al. 2012), which is accompanied by a worsening of the clinical condition, the appearance of signs of right ventricular heart failure. The risk of death in the event of cardiac arrhythmia in patients with PH increases by 1.75 times. Restoration of sinus rhythm leads not only to an improvement in the clinical condition, but also leads to a decrease in mortality (Olsson et al. 2013).

Methods for restoring sinus rhythm depend on the nature of rhythm disturbances and the clinical condition of the patient. In most patients with atrial flutter, catheter radiofrequency ablation is performed. After successful rhythm restoration by radiofrequency ablation, no additional antiarrhythmic therapy is usually required, while other methods of sinus rhythm restoration require anti-relapse therapy with amiodarone (Olsson et al. 2013; Grünig et al. 2018). If it is impossible to restore sinus rhythm, rhythm-reducing therapy is prescribed. To control the heart rate in atrial fibrillation, patients with PH are recommended to prescribe digoxin (Galiè et al. 2016; Kirchhof et al. 2016; Grünig et al. 2018).

In patients with decompensated PAH or end-stage PAH, cardiotoxic drugs may be prescribed as a symptomatic remedy to improve right ventricular contractility and maintain adequate perfusion pressure (Jentzer and Mathier 2015; Galiè et al. 2016; Condliffe and Kiely 2017).

Specific therapy

In the case of diagnosing PAH, one should start etiopathogenetic schemes for its correction as soon as possible. For this purpose, specific therapy methods have been developed based on the modern understanding of

endothelial dysfunction in pulmonary artery remodeling. The action of targeted therapy is associated with blockade of vasoconstrictor substance receptors and stimulation of major pathways mediated by potent vasodilators such as nitric oxide and prostacyclin (Figure 2) (Korokin et al. 2018).

Drugs from six different substance classes are currently being used to treat PAH in Europe. These drugs can be used singly or in combination. It must be remembered that pulmonary arterial hypertension remains an incurable disease. Thus, the goal of therapy is the localization of the disease, that is, the stabilization of the patient's condition at a satisfactory clinical level without signs of right ventricular failure and, ideally, without progression of the disease. In one randomized trial using initial combination therapy (Galie et al. 2015), this goal was achieved in 40% of patients. The choice of drug depends in part on the severity of pulmonary arterial hypertension, and current guidelines define (Galiè et al. 2015, 2016) it as low, moderate, or high risk based on expected mortality within one year. For patients with newly diagnosed "typical" PH and at low or moderate risk, initial or early combination treatment is used, including an endothelin receptor antagonist (ERA) with a phosphodiesterase-5 (PDE-5) inhibitor or a soluble guanylate cyclase (sGC) stimulator.

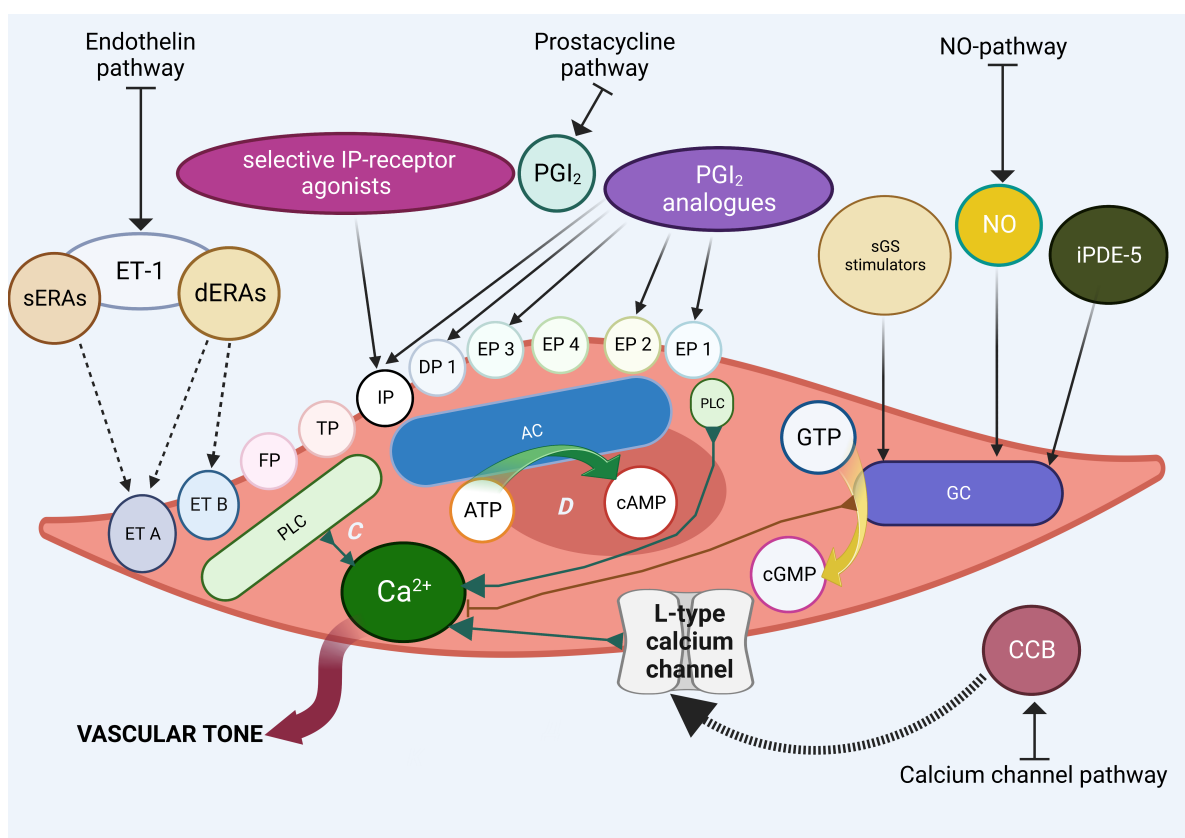


Figure 2. Pathways of action of various specific drugs on the tone of vascular smooth myocytes in PH. **Note:** cERAs - selective endothelin-1 receptor antagonists, dERAs - dual endothelin-1 receptor antagonists, ET A - endothelin type A receptor, ET B - endothelin type B receptor, FP - prostaglandin F receptor, TP - thromboxane receptor, CA IP receptors - selective agonists of prostaglandin I2 (prostacyclin) receptors, IP - prostaglandin I2 (prostacyclin) receptor, PGI₂ - prostaglandin I2 (prostacyclin), DP 1 - type 2 prostaglandin D2 receptor, EP 1-4 - prostaglandin E2 1-4 receptor type, PG E2 - prostaglandin E2, sGC - soluble guanylate cyclase, NO - nitric oxide, iPDE-5 - phosphodiesterase type 5 inhibitors, PLC - phospholipase C, AC - adenylate cyclase, ATP - adenosine triphosphate, cAMP - cyclic adenosine monophosphate, GTP - guanosine monophosphate, cGMP - cyclic guanosine monophosphate, BMCK - blockers of slow calcium channels), K - effect of vasoconstriction, D - effect of vasodilation. The arrows on the light part of the scheme: "with a crossbar on the tail" - indicate the main target of the path; "with shading on the body" - a negative impact; "with a transparent tail" - a positive impact. The number of scientific papers on the topic of pulmonary hypertension on the PubMed Internet resource in the period from 2000 to 2022.

Blockers of "slow" calcium channels

If patients with idiopathic, hereditary, or drug-induced pulmonary arterial hypertension test positive for vasoreactivity during right heart catheterization (decrease in mean PAP from more than 10 mm Hg to a level not exceeding 40 mm Hg, without reducing cardiac output), calcium antagonists, individually titrated to high doses, should be given first (Galiè et al. 2015; Simonneau et al. 2019). The choice of CCB may be influenced by increased heart rate or the presence of concomitant arterial hypertension: in the first case, *diltiazem* can be prescribed, in the second - *amlodipine* or *nifedipine*. *Verapamil* is not recommended for use in patients with PAH due to the presence of a negative inotropic effect. CCB therapy begins with a minimum dosage, gradually increasing the dosage to the maximum tolerated, given the possibility of developing systemic hypotension and edematous syndrome. In the most favorable case, this leads to the normalization of pulmonary hemodynamics. For patients with PAH who meet the criteria for a positive vasodilating response and are treated with calcium antagonists, every 3-4 months, fully reassess their condition and the effectiveness of ongoing therapy. In the absence of an adequate response in the form of a decrease in the functional class in combination with a pronounced improvement in hemodynamics (close to normal), additional therapy should be prescribed. However, this treatment regimen is suitable for less than 5% of the total number of patients with PAH (Galiè et al. 2015; Galiè et al. 2016). The practice of using calcium antagonists without a preliminary test for vasoreactivity is outdated.

For vasoreactivity-negative patients and those at high risk, combination therapy is recommended, including targeted drugs for specific PH therapy (Barst et al. 1996).

Endothelin-1 antagonists

Endothelin-1 (ET-1) is a peptide of endothelial origin that has two receptor subtypes, designated endothelin A (ETRA) and endothelin B (ETB), located on smooth muscle cells of the pulmonary arteries. ET-1 is a potent pulmonary vasoconstrictor and stimulates arterial smooth muscle cell mitosis, thereby promoting pulmonary vascular remodeling. Pulmonary and plasma levels of ET-1 are elevated in human PAH and in experimental animal models of PAH.

Binding of endothelin-1 to endothelin A and B receptors on pulmonary artery smooth muscle cells promotes cell proliferation and vasoconstriction (Clozel et al. 2013). Endothelin B receptors are predominantly expressed on pulmonary endothelial cells, promoting vasodilation through accelerated production of *prostacyclin* and *nitric oxide* and excretion of endothelin-1 (Clozel et al. 2013). However, selective blockade of only endothelin A receptors and non-selective blockade of both types of receptors have shown similar efficacy in PAH (Clozel et al. 2013). At the same time, it must be remembered that endothelial receptor antagonists are teratogenic and should not be used during pregnancy (Xing et al. 2017).

Currently, the following drugs from the group of endothelin-1 antagonists are used for the treatment of PAH:

Ambrisentan is an oral ERA drug that preferentially blocks endothelin A receptors. It has been shown to be effective in patients with PAH with respect to symptoms,

exercise, hemodynamics, and time to clinical deterioration (Galiè et al. 2008). However, subsequent studies have shown that the use of this drug is associated with an increase in the incidence of peripheral edema, while an increase in the frequency of liver dysfunction was not observed (Galiè et al. 2015).

Bosentan is an oral, non-selective ET antagonist that improves exercise performance, hemodynamics, and time to clinical deterioration in patients with PAH. When using this drug, it must be taken into account that in 10% of patients treated with *bosentan*, there is a reversible dose-dependent increase in hepatic transaminases (Humbert et al. 2007). It follows that in such patients, monthly monitoring of liver function should be carried out (Humbert et al. 2007). Moreover, due to pharmacokinetic interactions, *bosentan* may reduce the effectiveness of hormonal contraceptives, as well as reduce the levels of *warfarin*, *sildenafil* and *tadalafil* in serum (van Giersbergen et al. 2006; Wrishko et al. 2008).

Macitentan is an oral, non-selective ERA that improves physical performance in PAH patients and prevents disease progression (Pulido et al. 2013). Despite the absence of hepatotoxicity, 4.3% of patients experienced a decrease in Hb levels to ≤ 80 g/l, during therapy with 10 mg *macitentan* (Pulido et al. 2013).

PDE-5 inhibitors

Phosphodiesterases (PDEs) are a complex family of intracellular enzymes isolated in the early 1970s from rat brain by polyacrylamide gel electrophoresis, which hydrolyze 3', 5'-cyclic nucleotide monophosphates into the corresponding 5'-monophosphates (Francis et al. 2001), i.e. cause degradation of (adenosine monophosphate) cAMP and guanosine monophosphate (cGMP). Thus, PDEs balance the work of effector enzymes - adenylylase and guanylylase, which catalyze the formation of cAMP and cGMP from ATP and GTP, respectively. This is the basis for the most important role of PDEs in maintaining intracellular homeostasis and their influence on cellular functions.

From the point of view of the chemical structure and functional features, it is customary to distinguish 11 types (families, isoenzymes) of PDEs (Jeon et al. 2005) involved in the implementation of various functional reactions of the body.

PDE-5 is overexpressed in PH patients (Nagendran et al. 2007), and *sildenafil*, as the first PDE-5 inhibitor, significantly improves pulmonary vasorelaxation (Rubin et al. 2011). It acts on the NO-dependent pathway of pulmonary vasodilation by inhibiting phosphodiesterase type 5 (cGMP-dependent). An increase in the level of intracellular cGMP, a secondary messenger of endogenous *nitric oxide*, stimulates vasodilation in the pulmonary vessels by relaxing the smooth muscle cells of the vascular wall and inhibits their proliferation due to the activation of cGMP-dependent peptidkinases and potassium channels (Martynyuk et al. 2015). Thus, cGMP is considered as a unique target molecule in PH. PDE-5 is also abundantly expressed in platelets, and its inhibition reduces platelet aggregation. Insufficient NO-cGMP signal leads to pulmonary thrombosis and platelet activation, which is a common clinical manifestation of PH (Dunkern et al. 2005; Gudmundsdóttir et al. 2005). Treatment with *sildenafil* has been shown to increase the

sensitivity of platelets to NO, which prevents platelet aggregation (Mullershausen et al. 2004). It is worth noting that sildenafil, tadalafil, and vardenafil increase pulmonary vasorelaxation in a dose- and time-dependent manner, with vardenafil having a maximum effect after 40-45 minutes, sildenafil after 60 minutes, and tadalafil after 75-90 minutes. The results of clinical trials SUPER-1 (double-blind study) and SUPER-2 (open study) in patients with PH showed a positive effect of treatment with sildenafil. Hemodynamic parameters, which include total mean pulmonary artery pressure, pulmonary vascular resistance, and 6-minute walk test results, were significantly improved. In addition, one-year survival was 96% in patients with IPAH, which is 71% higher than expected survival. The REPLACE trial to replace riociguat, a soluble guanylate cyclase stimulator, with sildenafil was positive and supported the hypothesis of PDE-5 inhibition as a treatment option in patients with PH with an intermediate risk of mortality within 1 year (Tsareva and Avdeev 2013; Koklin and Danilenko 2019; Hoepfer et al. 2021; Liu et al. 2023). Sildenafil and tadalafil are FDA approved for the treatment of PAH and are used to reduce mortality either as monotherapy or in combination with prostacyclin analogues or endothelin-1 receptor blockers.

Although none of the studies directly compared vardenafil, tadalafil, and sildenafil, a positive effect of PDE-5 inhibitors was seen in all three of the above drugs. However, the effect size seemed larger for sildenafil compared to vardenafil and tadalafil, possibly due to the large number of studies that included the drug sildenafil. In the Russian Federation, only one IFDE-5 drug, sildenafil, is registered for the treatment of PAH.

cGMP production stimulator - Riociguat

Riociguat, as a sGC stimulator, unlike PDE-5 inhibitors that slow down the degradation of cGMP, enhance its production by directly stimulating the enzyme, both in the presence and in the absence of endogenous NO (Schermyly et al. 2011).

Riociguat has a dual mechanism of action: it sensitizes sGCs to endogenous NO by stabilizing their binding, and also directly enhances cGMP production by directly stimulating the enzyme, both in the presence and absence of endogenous NO, which is significantly reduced in PAH patients. Due to these effects, riociguat restores the metabolic pathway "NO - sGC - cGMP" and causes an increase in the production of cGMP, which plays an important role in the regulation of vascular tone, proliferation processes, fibrosis and inflammation (Ghofrani et al. 2016).

The study demonstrated that patients with PAH treated with riociguat up to 2.5 mg intravenously showed favorable results in terms of physical performance, hemodynamics, and time to clinical deterioration (Ghofrani et al. 2013). Riociguat has a good safety spectrum, as the frequency of the most serious adverse events, such as syncope, did not fundamentally differ from the placebo group at the maximum dosage. Before starting therapy, the patient must give up cigarettes, since the concentration of riociguat in the blood decreases significantly against the background of smoking. Riociguat has a teratogenic effect and its use in pregnant women is contraindicated.

Prostacyclin analogues

Prostacyclin (prostaglandin I₂) is a potent pulmonary vasodilator that acts via the cAMP pathway. It has been shown that in PAH, the production of prostacyclin in endothelial cells is significantly reduced, which in turn leads to vasoconstriction, proliferation of smooth myocytes and platelet aggregation, which can lead to both the development and aggravation of this pathological condition. Three prostacyclin analogs are currently available: epoprostenol, iloprost, and treprostinil.

The first synthetic drug, epoprostenol, has shown significant efficacy as a therapeutic agent in improving hemodynamic parameters, exercise performance, and mortality. However, it is not without its shortcomings. Its short half-life requires continuous intravenous infusion through a central venous catheter, which requires central line placement and potentially poses a risk of central line infection. The initial preparations were required to be stored in the refrigerator or on ice; however, newer drugs have a more stable half-life of 24 hours (Kallen et al. 2008; Sitbon et al. 2014; Sitbon and Vonk Noordegraaf 2017).

Iloprost is a chemically stable prostacyclin analogue that is most commonly used by inhalation. In the Russian Federation, only iloprost is registered from this group, which is used on average 6-9 times a day using an ultrasonic nebulizer at a dose equivalent to the content of 2.5-5 µg of the drug at the level of the alveoli, as part of specific combined therapy. The efficacy of inhaled iloprost was evaluated in the AIR-1 short-term RCT in patients with PAH and inoperable forms of CTEPH with FC III-IV (NYHA). During therapy with iloprost, there was a significant improvement in hemodynamic parameters, an increase in exercise tolerance and a decrease in PAH FC. However, long-term iloprost monotherapy did not result in improved survival and morbidity (Opitz et al. 2005). Therefore, at present, iloprost is used only as part of a specific combination therapy in addition to oral drugs (Hoepfer et al. 2006; McLaughlin et al. 2006; Zheng et al. 2014). Side effects include headaches, hot flashes, and jaw pain. In addition, in patients with broncho-obstructive syndrome, against the background of inhaled iloprost, the reactivity of the upper respiratory tract may increase and cough may appear. Iloprost has a pronounced antiplatelet effect, so its use in patients with bleeding is contraindicated.

Treprostinil is a tricyclic benzidine thermostable analog of epoprostenol. Chemical stability allows you to prescribe the drug intravenously and subcutaneously. The effects of treprostinil were studied in randomized clinical trials and were characterized by improvement in physical abilities, hemodynamics and symptoms.

Prostacyclin (IP) receptor agonists

Selexipag is a long-acting oral selective non-prostanoid prostacyclin receptor (IP) agonist indicated for the treatment of symptomatic pulmonary arterial hypertension (PAH) in adults. It was designed to overcome the pain associated with standard prostanoid therapy, presenting fewer side effects and comparable hemodynamic benefits.

Stimulation of IP receptors by selexipag leads to vasodilation, as well as antiproliferative and antifibrotic effects.

The active substance prevents remodeling of the heart and lungs in rats with pulmonary PAH and causes a proportional decrease in pulmonary and peripheral pressure, showing that peripheral vasodilation reflects pharmacodynamic efficacy in relation to pulmonary vessels.

Selexipag is metabolized by the cytochrome P450 system (CYP 2C9 and 3A4), which can lead to the formation of a toxic intermediate and can also cause drug interactions, especially with cyclosporine A.

Selexipag has been shown to be effective in improving the combined morbidity-mortality outcome in adult patients with PAH (primarily idiopathic connective tissue disease secondary to corrected congenital heart disease) WHO FC II and III as monotherapy or as an adjunct to an endothelin receptor agonist or a phosphodiesterase 5 inhibitor (Panagiotidou et al. 2021).

In clinical practice, **selexipag** is mainly used when patients have an inadequate response to initial oral combination therapy with an endothelin receptor agonist and a PDE-5 inhibitor. **Selexipag** is not equivalent to parenteral **prostacyclin** and is not intended to replace its use in high-risk patients (Genecand et al. 2021).

Other specific therapies

Response to specific therapy is usually assessed after 4-12 weeks and then at intervals of 3 to 6 months. Further correction of the treatment regimen should be purely individual. If the main therapeutic goal has not been achieved - the patient has not moved into the low-risk category, after the initial treatment, the next step is a double or triple combination treatment. Combination therapy is an attractive approach due to the possibility of simultaneous influence on several pathways of PAH pathogenesis, which leads to a decrease in PVR, prevention of further remodeling of the pulmonary arteries and, as a result, to an increase in the time until the course of PAH worsens, and a decrease in the incidence of complications, including fatal ones.

If the response to treatment is still inadequate, evaluation for lung transplantation should be started immediately, as decompensation can occur quickly and without warning in such patients. Although the majority of patients with pulmonary arterial hypertension currently do not require transplantation, this measure is indispensable for those whose pathology has proven resistant to conservative methods of treatment. Combined heart and lung transplantation is only necessary in exceptional cases, as right heart function almost always returns to normal after lung transplantation (Crovetto et al. 2016). In recent years, the results of lung transplantation have shown significant progress, and now experienced centers report a one-year survival > 90% (Tudorache et al. 2015).

As an operative, but less radical method of treatment, fluoroscopically guided denervation of the pulmonary artery (PADN) can be used. This procedure is aimed at correcting the sympathetic regulation of pulmonary vascular tone in PAH. In single-center clinical studies, this method has been associated with a reduction in PAP and an improvement in right ventricular function (Chen et al. 2013). However, the adaptation of PADN to routine clinical practice has so far been limited by the lack of multicentre clinical trials in PAH, the lack of unique expertise required for successful ablation, and uncertainty

about its efficacy compared to placebo or drug therapy in PAH.

Right atrial pacing has been used to alleviate right ventricular failure in patients after myocardial infarction. In PAH, chronotropic insufficiency is associated with impaired cardiac output. Recent clinical data from patients with PAH (Khural et al. 2021) have shown that right atrial pacing significantly reduced end-diastolic pressure and right ventricular volume and increased cardiac output to normal levels. However, this and similar methods still need deeper study and additional tests.

The management of patients with “atypical” PAH is less standardized. Treatment of most of these patients, as a rule, begins with monotherapy with PDE-5 inhibitors (Opitz et al. 2016). Further adjustment of the treatment regimen depends on the response and individual circumstances; due to the lack of complete data for this type of pathology, at the moment there are no general recommendations for the management of such patients. Due to age and the presence of comorbidities, most patients with “atypical” PAH are usually not candidates for lung transplantation.

Promising areas of research in the field of PH therapy

Departing from standardized in most countries targeted drugs for the treatment of PAH, it is worth noting that in recent years many new specific drugs and methods for its therapy have been discovered. Recent studies have shown that the Rho-kinase inhibitor **fasudil** improves the acute hemodynamics of congenital heart disease with severe pulmonary hypertension in a dose-dependent manner (Ruan et al. 2019). In addition, studies have shown that **silibinin**, an inhibitor of CXCR4, can attenuate PAH and reduce phases of pulmonary arterial pressure, however, this was not effective in the advanced stages of the disease (Zhang et al. 2019). Moreover, **silibinin** can delay pulmonary artery occlusion and pulmonary vascular remodeling by inhibiting the CXCR4/SDF-1 axis (Zhang et al. 2019). At the same time, the efficacy, durability, safety, and long-term clinical impact of these specific drugs in patients with PAH need further evaluation.

Prostanoids are a promising group of drugs for the treatment of PAH, since they have not only vasodilating, but also antiplatelet and antiproliferative effects. Currently, prostacyclins remain the mainstay of PAH treatment. However, there is another mechanism of vasoconstriction of the vessels of the pulmonary circulation, it is associated with inhibition of the formation of prostaglandins (primarily prostaglandin E2), which normally have a vasodilating effect (Ostroumova et al. 2022). The prostacyclin (IP) receptor, prostaglandin E3 (EP3) receptor and prostaglandin E4 (EP4) receptor are the main pulmonary artery receptor subtypes in both rat and human pulmonary arteries. Patients with PH have decreased levels of circulating PGI₂ and PGE₂. PGE₂ is a potent vasodilator, although it may have a vasoconstrictive effect in some cases. In many vascular preparations, including mouse aortic annulus, rabbit ductus arteriosus, human pulmonary vein, PGE₂ directly relaxes tissues precompressed with KCl or norepinephrine with nearly two orders of magnitude greater efficiency than PGI₂ (IP) or PGD receptor activation. 2 (DP) (Ostroumova et al. 2022).

The biological action of PGE₂ is mediated by G protein-coupled E-prostanoid receptors, EP₁, EP₂, EP₃

and EP₄. These four EP receptor subtypes are associated with different signaling pathways. In general, EP₁/EP₃ receptors have a vasoconstrictive and prohypertensive effect, while EP₂/EP₄ receptors have a vasodilating and antihypertensive effect (Sugimoto et al. 2007). In connection with the above, the development of drugs for EP₃ antagonists and EP₄ agonists can become a new promising direction in the treatment of PH. Also, in patients with PAH, there is often a violation of bronchodilation, which is mediated specifically by the EP₄ receptor. Respiratory function is one of the key parameters in patients with PH, drugs that cause bronchorelaxation and reduce hypoxia can be of great benefit to patients with PH.

Nitric oxide (NO) is the most important vasodilator of endothelial origin and numerous studies have found that its concentrations are reduced in patients with PH (Sausbier et al. 2000). Recent studies show that NO donor drugs such as diethylamine-NO, sodium nitroprusside, monoorganic nitrite can be very effective in patients with PH due to its natural vasodilating properties (Mondéjar-Parreño et al. 2019; Hurtsén et al. 2020).

The action of most of the above drugs is based on the restoration of endothelial function through the restoration of the balance of vasoconstrictors and vasodilators. However, due to the fact that the pathogenesis of PAH and many other forms of PH is endothelial dysfunction, which is manifested by oxidase (or oxidative) stress, antioxidant drugs may become a promising direction in the treatment of PH (Simonneau et al. 2019).

For example, recent studies have shown that alginate oligoside (AO) acts as an antioxidant and anti-inflammatory agent in PAH by inhibiting monocrotaline-induced pulmonary vascular remodeling. AO also reduces the expression of malondialdehyde and pro-inflammatory cytokines, while increasing the expression of anti-inflammatory cytokines (Feng et al. 2020). Sulforaphane reduces pulmonary vascular remodeling, inflammation and fibrosis (Kang et al. 2020). Oral melatonin given to mother sheep late in pregnancy improved lambs' pulmonary vascular function, stimulated antioxidant activity, and reduced reactive oxygen species and nitrotyrosine, a marker of oxidative stress in small pulmonary vessels (Astorga et al. 2018; Gonzalez-Candia et al. 2019;). Oral administration of seloncertib resulted in a dose-dependent decrease in pulmonary artery pressure and right ventricular hypertrophy in a model of PAH (Boucherat et al. 2018; Budas et al. 2018).

In addition, multiple studies have led to the emergence of other equally promising therapeutic approaches in the field of PAH. Thus, recent scientific work has shown that regenerative cell therapy, gene therapy, and epigenetic drugs can offer a new perspective in the treatment of PAH (Baliga et al. 2011; Loisel et al. 2018;).

It has been shown that damage and dysfunction of the endothelium in PAH conditions cause disruption of apoptosis processes in endotheliocytes and stimulate the formation of obliterating plexiform lesions (Sakao et al. 2009). Cell alteration and subsequent endothelial dysfunction may, in turn, cause loss of the distal, most functional pulmonary vessels. Stem cell therapy aims to repair endothelial damage and dysfunction while at the same time repairing the distal pulmonary vasculature (Weiss et al. 2011). As the main types of stem cells used

in therapy, the following are distinguished: endothelial progenitor cells (EPC); mesenchymal stem cells (MSCs) and pluripotent stem cells (PSCs) (Weiss et al. 2011).

EPCs were first derived from mononuclear cells in 1997, after which their rapid study began (Yoder 2012). This discovery showed that angiogenesis can occur post-embryogenesis from a population of cells other than angioblasts (Foster et al. 2014).

In preclinical studies, EPC administration has demonstrated the ability of these cells to engraft in the distal pulmonary arterioles and to significantly slow down or completely prevent disease progression in rat models of PH. When administered 3 days after injection of monocrotaline to rats, EPC significantly reduced the pressure in the right ventricle of the heart. This study was the first to present the possibilities of not only therapeutic but also prophylactic use of EPA. It should also be noted that rats treated with EPC transduced with human endothelial nitric oxide synthase (eNOS) showed a significant change in PAP in the monocrotaline-induced PH model. In addition, EPC delivery successfully prevented the onset of PAH in athymic rats (Zhao et al. 2005).

Recent studies have shown the possible efficacy of cell therapy based on the enhancement of BMPR2 signaling, the activation of which suppresses the rapid expansion of blood vessel smooth muscle tissue, which contributes to the life support of pulmonary arterial endothelial cells and the prevention of arterial damage (Harper et al. 2019). To do this, the researchers used EPCs transduced with adenovirus vectors and carrying the luciferase reporter gene and GFP (AdTrackLuc) or BMPR2 (AdCMVBMPR2myc) obtained from the bone marrow of rat femurs. Using the monocrotaline-induced PAH model, rats were injected into the tail vein after the onset of signs of PH. The authors found that injections of these cells significantly increased BMPR2 expression and signaling in the lungs by the end of the first day after injection. Overall, this study has shown the therapeutic efficacy of enhancing BMPR2 signaling, which may be of great importance for future translational studies.

In 2007, a pilot randomized control trial was conducted in 31 patients with idiopathic PAH after successful trials in laboratory animals to evaluate the safety and efficacy of EPC therapy in humans. Patients treated with EPC in addition to conventional therapy showed significant improvement in 6-minute walk test, mean PAP, PVR, and cardiac output at 12 weeks, while no side effects were identified (Wang et al. 2007). A small pilot study was also conducted in children with IPAH and showed improvement in hemodynamic parameters, exercise tolerance and quality of life after 12 weeks (Zhu et al. 2008). It is worth noting that in order to reliably confirm such efficacy and safety, additional, more extensive studies with long-term follow-up are needed before they are included in the main structure of the treatment of PH.

In 2015, the aim of the Pulmonary Hypertension and Angiogenic Cell Therapy (PHACeT) study was to investigate the tolerability of cultured eNOS-transfected EPCs in PAH patients who had failed other methods (Granton et al. 2015). Patients received 3 doses of eNOS-transfected EPCs (eNOS-transfected EPCs) injected into the right atrium for several consecutive days. The results showed that such therapy is well

tolerated and improves hemodynamics in the short term.

MSCs have been widely studied in recent years and successfully used to treat various diseases (Lalu et al. 2012). The source of these cells is usually adipose tissue and Wharton's jelly. MSCs have pronounced regenerative properties and play a significant role in tissue repair and angiogenesis. It has been shown that, when introduced into tissues, they migrate to the sites of damage, differentiate, and contribute to their recovery (Suen et al. 2013).

Recent studies report several benefits of using MSCs as a stem cell transplant. Firstly, they are quite easily cultivated and are immunologically compatible since the main histocompatibility complex is absent in their structure. Secondly, they have demonstrated anti-inflammatory, pro-angiogenic, and anti-apoptotic properties, which makes the use of MSCs promising (Foster et al. 2014). In a rat model of pulmonary hypertension, intravenous administration of MSCs after PH induction with monocrotaline reduced right ventricular systolic pressure, medial thickening, and suppressed pulmonary collagen synthesis along with anti-inflammatory and anti-apoptotic markers (de Mendonca et al. 2017). Moreover, MSCs simultaneously reduced right heart hypertrophy and normalized right ventricular ejection fraction in a monocrotaline-induced PAH model in rats (Umar et al. 2009).

iPSCs are adult somatic cells that, through genetic reprogramming (through the transduction of certain transcription factors), have acquired the characteristics of embryonic stem cells. The results of a 2016 study of the therapeutic potential of iPSCs in rats with monocrotaline-induced PH showed that rats with PH treated with iPSCs had a marked improvement in hemodynamic parameters (Huang et al. 2016). Histological examination additionally confirmed the favorable effect of iPSCs on the degree of remodeling of small-caliber pulmonary arteries. Thus, in rats treated with iPSCs, a significant decrease in hypertrophy of the media was observed. In addition, immunohistochemical analysis showed that the use of this kind of stem cells significantly suppressed inflammation in the lungs of rats with monocrotaline-induced PH (Huang et al. 2016). However, it is important to emphasize that iPSC regimens still require further optimization and further study before clinical use.

Various genetic defects can potentiate the occurrence of PH through various mechanisms, such as resistance to apoptosis or impaired calcium metabolism (Lee and Young 2013). It follows that the development of efficient harmless gene delivery systems is a promising approach to the treatment of PAH. A large number of experimental studies have demonstrated that the delivery of targeted drugs that can influence the degree of gene expression can be used both for the treatment and prevention of the onset of the disease (Reynolds 2011).

Of the many mechanisms of delivery of gene agents in the case of PAH, endotracheal administration by aerosol has the greatest promise, acting on endothelial and smooth muscle cells of the pulmonary arteries, as well as on connective tissue cells. This method remains non-invasive and prevents the degradation of nucleic acids by reducing endonuclease activity (Katz et al. 2019). In addition, direct delivery through the respiratory tract causes little to no systemic side effects and allows the agents not to undergo primary metabolism in the liver.

Genetic studies have identified more than 450 heterozygous germline mutations in the bone morphogenetic protein receptor type 2 (BMP2) gene (Fessel et al. 2011). Reduced BMP2 expression has also been reported in rodent models of monocrotaline-induced pulmonary hypertension. Moreover, the association of mutations in this gene or its low expression with the progression of PH has been identified in several scientific papers (Austin and Loyd 2014).

In 2013, a study identified the compound FK506 (tacrolimus). This compound activates BMP2-mediated signaling and regulation of endothelial-specific genes. This compound reversed severe hypertension in a rat model of monocrotaline-induced PH, as well as in a conditional deletion of BMP2 mouse model, as evidenced by reductions in right ventricular systolic pressure, PAP, medial hypertrophy, and neointimal formation (Spiekerkoetter et al. 2013). This efficacy stimulated further work in the direction of studying the safety of using FK506 in patients with PAH, which showed rather conflicting results (Spiekerkoetter et al. 2015).

Another approach to therapy associated with BMP2 is associated with the restoration of signaling of this gene based on the direct effect of BMP9, its ligand, on target cells (Long et al. 2015). A 2015 study showed that BMP9 endothelial pretreatment prevents endothelial cell apoptosis. This study also demonstrated that daily intraperitoneal administration of BMP9 reversed PAH in a mouse model carrying a heterozygous knockdown of the R899X mutation of human BMP2-II (Long et al. 2015).

Another study showed that targeted delivery of an adenoviral vector containing the BMP2 gene is effective as a therapy for hypoxic pulmonary hypertension in experimental rodent models (Reynolds et al. 2007). The authors found that delivery of the BMP2 gene significantly reduces the degree of morphological changes, as well as pressure in the right ventricle and pulmonary artery (Reynolds et al. 2007). However, the adenoviral vector itself is a limiting factor for both research and clinical use. In particular, numerous studies have shown that the use of such vectors is associated with an inflammatory response (Lee et al. 2017).

In recent years, more and more different genes have been identified that are involved in the etiology or pathogenesis of PH. Along with their identification, work is slowly beginning to explore the potential use of such genes as new etiopathogenetic treatments (Table 1).

Over the years, more and more studies have shown that epigenetic factors play a significant role in the etiopathogenesis of PAH (Cheng et al. 2019; Bissierier et al. 2020). Epigenetics is defined as an inherited change in gene expression without changing the DNA sequence (Weinhold 2006). Such changes are partly mediated by specific epigenetic modifications (epigenetic marks) and are represented by processes such as methylation, acetylation, or phosphorylation of DNA/histone proteins. Such changes can affect the degree of chromatin condensation, transcription processes, and the intensity of gene expression (Weinhold 2006). For example, several studies have reported hypermethylation of the BMP2 promoter gene in blood mononuclear cells in patients with hereditary PAH using genomic bisulfite sequencing (Liu et al. 2017).

Table 1. Research work on the topic of gene therapy correction of PH

An investigational method for the correction of pulmonary hypertension	Experimental model	Effects	Source
1. Gene: Tagln Delivery method: lentoviral vector Method of administration: intratracheal	Hypoxic pulmonary hypertension in rats	Decreased right ventricular systolic pressure and vascular remodeling	Zhang et al. 2014
2. Gene: Gal-3 Delivery method: lentoviral vector Method of administration: intratracheal	Monocrotaline-induced pulmonary hypertension in rats	Decrease in systolic pressure in the right ventricle, decrease in right ventricular hypertrophy	Li et al. 2019
3. Gene: Twist1 Delivery method: lentoviral vector Method of administration: Delivery of cells from fibrin gel	Hypoxic pulmonary hypertension in mice	Prevention hypoxia-induced endothelial-mesenchymal transition	Mammoto et al.2020
4. Gene: CD40 Delivery method: lentoviral vector Route of administration: intravenous	Monocrotaline-induced pulmonary hypertension in rats	Decrease in mean pulmonary arterial pressure, decrease in right ventricular systolic pressure, decrease in right ventricular hypertrophy	YanYun et al. 2015
5. Gene: HIF-1 α Delivery method: lentoviral vector Route of administration: intratracheal	Hypoxic pulmonary hypertension in rats	Decrease in systolic pressure in the right ventricle, decrease in right ventricular hypertrophy	Li et al. 2016
6. Gene: Tph1 Delivery method: adenovirus vector Route of administration: intravenous	Hypoxic pulmonary hypertension in rats	Decrease in systolic pressure in the right ventricle, decrease in right ventricular hypertrophy, decrease in the degree of remodeling of the vessels of the pulmonary circulation	Morecroft et al. 2012
7. Gene: CGRP (AdRSVCGRP) Delivery method: adenovirus vector Route of administration: intratracheal	Hypoxic pulmonary hypertension in mice	Decreased pulmonary arterial pressure (PAP), pulmonary vascular resistance, right ventricular hypertrophy, and pulmonary vascular remodeling	Bivalacqua et al. 2002
8. Endothelial NO synthase gene (AdCMVceNOS) Delivery method: adenovirus vector Route of administration: intratracheal	Hypoxic pulmonary hypertension in rats	Restoration of NO production in the vessels and a decrease in the formation of neointima, a decrease in the remodeling of the vessels of the pulmonary circulation, decreased pulmonary arterial pressure (PAP), pulmonary vascular resistance, right ventricular hypertrophy	Janssens et al. 1996
9. Gene: Kv1.5 KCNA5 Delivery method: adenovirus vector Route of administration: intratracheal	Hypoxic pulmonary hypertension in rats	Decrease in systolic pressure in the right ventricle, decrease in right ventricular hypertrophy	Pozeg et al. 2003
10. Gene: Forkhead box O (FoxO1) Delivery method: adenovirus vector Route of administration: orotracheal	Monocrotaline-induced pulmonary hypertension, hypoxic pulmonary hypertension, hypoxia + SU5416-induced pulmonary hypertension in rats	Decreased pulmonary arterial pressure, pulmonary vascular resistance, right ventricular hypertrophy, and pulmonary vascular remodeling	Savai et al. 2014
11. Gene: VEGF (VEGF 165 human) Delivery method: adenovirus vector Route of administration: intratracheal	Hypoxic pulmonary hypertension in rats	Increased activity of endothelial nitric oxide synthase in the lung tissue, restoration of endothelium-dependent vasodilation, decreased systolic pressure in the right ventricle, decreased right ventricular hypertrophy	Partovian et al. 2000
12. Gene: Angiostatin (Ad.K3) Delivery method: adenovirus vector Route of administration: intratracheal	Hypoxic pulmonary hypertension in mice	Aggravation of the development of PH Enhance remodeling Increased pressure in the right ventricle	Pascaud et al. 2003
13. Gene: BMPR2 Delivery method: adenovirus vector Route of administration: intravenous	Hypoxic pulmonary hypertension in rats	Decrease in mean pulmonary arterial pressure, decrease in right ventricular systolic pressure, decrease in right ventricular hypertrophy	Reynolds et al. 2007
14. Gene: sTIE2 Delivery method: adeno-associated viral vector Route of administration: into the pulmonary artery	Monocrotalin-induced pulmonary hypertension in rats; pulmonary hypertension by increasing the expression of angiotensin II in the smooth muscles of the pulmonary vessels; hypoxic pulmonary hypertension in rats	Lack of proliferation of smooth muscle cells in the arterioles of the lungs, the absence of occlusion of small pulmonary vessels in monocrotaline and angiotensin II-induced pulmonary hypertension	Kido et al. 2005
15. Gene: human PGIS (hPGIS) Delivery method: adeno-associated viral vector Route of administration: intramuscular	Hypoxic pulmonary hypertension in mice Monocrotaline-induced pulmonary hypertension in rats	Decrease in systolic pressure in the right ventricle, decrease in RV hypertrophy Decreased vascular remodeling of ICC	Kawakami et al. 2007
16. Human gene: SERCA2a Delivery method: adeno-associated virus serotype 1 (AAV1) Route of administration: intratracheal	Rats with monocrotaline-induced pulmonary arterial hypertension	Reduced pulmonary artery pressure, decreased vascular remodeling, right ventricular hypertrophy, and fibrosis	Hadri et al. 2013
17. Human gene: SERCA2a Delivery method: adeno-associated virus serotype 1 (AAV1) Route of administration: intratracheal	Yorkshire pigs with partial pulmonary vein bandage	Decrease in pulmonary artery remodeling with concomitant improvements in pulmonary hemodynamics and right ventricular function	Aguero et al. 2016
18. Human prostacyclin synthase gene Route of administration/delivery: transfection into the liver	Rats with monocrotaline-induced pulmonary hypertension	Improvement in the condition caused by pulmonary hypertension and higher survival	Suhara et al. 2002
19. Human prostacyclin synthase cDNA (hPGIS) Delivery method: luminal adeno-associated virus serotype 9 Route of administration: into the lungs	Rats with monocrotaline-induced pulmonary arterial hypertension	Significant reduction in PAH severity, prevention of cardiac and pulmonary vascular remodeling	Gubrij et al. 2014
20. SERCA2a gene Delivery method: aerosolized AAV1.S2a Administration method: intratracheal	Rats with monocrotaline-induced pulmonary arterial hypertension	Decreased myocardial remodeling and susceptibility to ventricular tachycardia in palpitations	Strauss et al. 2019
21. SERCA2a gene Delivery method: aerosolized AAV1.S2a Administration method: intratracheal	Lung tissue from patients with idiopathic PAH. Rats with monocrotaline-induced PAH	Weakening of remodeling and resistance of pulmonary vessels and, inhibition of remodeling of the right ventricle of the heart and a significant restoration of its function	Bisserier et al. 2021
22. Class I HDAC inhibitor MS-275 (intra-abdominal infection) and miR-34a agomiR (tail vein infection)	Rats with monocrotaline-induced pulmonary arterial hypertension	Reduces pulmonary artery remodeling and worsening of PAH	Li et al. 2021

This led to a decrease in BMPR2 expression, which, in turn, could stimulate cell proliferation and provoke the development of PAH. In 2010, researchers found that levels of mitochondrial superoxide dismutase 2 (SOD2) were significantly reduced in FHR rats, in which PAH forms spontaneously (Archer et al. 2010). Since there were no changes in the sequence of the DNA chain, bisulfite sequencing of pulmonary vascular myocytes obtained from such rats was performed and revealed hypermethylation of CpG islands in the SOD2 promoter region. Inhibition of DNA methyltransferases by 5-aza-2'-deoxycytidine restored SOD2 expression, suppressed cell proliferation and resistance to apoptosis in rat pulmonary artery myocytes (Archer et al. 2010). Taken together, this study suggested that DNA methylation-specific targeted therapy may be a promising option for PAH inhibition.

Histone deacetylase (HDAC) is a class of enzymes that remove the acetyl group from histone proteins, affecting chromatin compaction and availability of transcription factors in DNA (Seto, Yoshida, 2014). This changes the mechanism of transcription and is usually associated with its suppression. Preliminary studies have shown that HDAC types 1 and 5 are elevated in patients with PAH and experimental PH models in laboratory animals (Zhao et al. 2012). In a rat model of monocrotaline-induced PH caused by pulmonary artery

ligation, HDAC (valporic acid) inhibitors have been shown to be beneficial, significantly reducing the rate of right ventricular remodeling (Cho et al. 2010). Similarly, compound MC1568 (selective HDAC class IIa inhibitor) inhibited monocrotaline-induced PH (Kim et al. 2015). Overall, these independent studies have further supported the therapeutic potential of using HDAC inhibitors to reduce histone acetylation.

Conclusion

Currently, there are multiple and multidirectional methods of treatment and correction of PH. However, despite the abundance of works devoted to the study of this pathology, pulmonary hypertension of any etiology remains, as a rule, an incurable condition that significantly reduces both the quality and life expectancy. In this regard, the search for new mechanisms of therapeutic effects, and at the same time new more effective treatment strategies, remains an important issue for public health and the scientific community.

Conflict of Interest

The authors declare no conflict of interests.

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