THE ROLE OF AN ENDOTHELIN RECEPTOR ANTAGONIST IN THE PATHOGENETIC TREATMENT OF PULMONARY ARTERIAL HYPERTENSION

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Abstract: *theoretical aspects of the using of endothelin receptor antagonists in the pathogenetic treatment of pulmonary hypertension are investigated. A comparative analysis of selective and non-selective endothelin receptor antagonists in the treatment of pulmonary arterial hypertension is performed. Special attention is paid to the role of endothelin in the pathogenesis of pulmonary hypertension. The pharmacodynamic and pharmacokinetic features of individual representatives of endothelin receptor antagonists, such as bosentan, ambrisentan and macitentan, the effect of these drugs on clinical symptoms, hemodynamic parameters, and load tolerance were studied.*

Keywords: *pulmonary arterial hypertension, endothelin receptor antagonists, antifibrotic effect, pulmonary vascular remodeling.*

РОЛЬ АНТАГОНИСТА РЕЦЕПТОРОВ ЭНДОТЕЛИНА В ПАТОГЕНЕТИЧЕСКОМ ЛЕЧЕНИИ ЛЕГОЧНОЙ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИИ

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Аннотация: *исследованы теоретические аспекты применения антагонистов рецепторов эндотелина в патогенетическом лечении легочной гипертензии. Проводится сравнительный анализ селективных и неселективных антагонистов рецепторов эндотелина в лечении легочной артериальной гипертензии. Отдельное внимание в статье уделяется роли эндотелина в патогенезе легочной гипертензии. Изучены фармакодинамические и фармакокинетические особенности отдельных представителей АРЭ, таких как бозентан, амбризентан и мацитентан, влияние этих лекарственных средств на клиническую симптоматику, гемодинамические параметры, толерантность к нагрузкам.*

Ключевые слова: *легочная артериальная гипертензия, антагонисты рецепторов эндотелина, антифибротический эффект, ремоделирование легочных сосудов.*

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Pulmonary hypertension (PH) is a pathophysiological condition that includes a variety of clinical conditions and complicates the course of most cardiovascular diseases and lung pathologies. LH is defined as an increase in mean pulmonary artery pressure (mPPA)> 25 mm Hg. at rest according to the data of catheterization of the right chambers of the heart (CPC) [1].

In the pathogenesis of the disease, four main pathophysiological phenomena should be distinguished:

- vasoconstriction.
- reduction of the pulmonary vascular bed.
- decreased elasticity of pulmonary vessels
- bliteration of pulmonary vessels (thrombosis in situ, proliferation) [7].

Current theories of PH pathogenesis focus on dysfunction or damage to the endothelium, leading to an imbalance between vasoconstrictive and vasodilating agents and the development of vasoconstriction. Endothelial cells are damaged, and unidentified chemotactic agents are released from these cells, which cause migration of smooth muscle cells into the intima of the pulmonary arterioles. The secretion of locally active mediators with a pronounced vasoconstrictor effect contributes to the development of thrombosis in situ, transforming the state of the pulmonary vascular bed from the usual anticoagulant state due to the release of prostacyclin and an inhibitor of tissue plasminogen activator into a procoagulant state. As a result, a vicious

circle is formed: damage to the endothelium is steadily progressing and leads to remodeling of pulmonary vessels, an increase in vascular obstruction and obliteration. In this case, pathological processes affect all layers of the vascular wall, various types of cells - endothelial, smooth muscle, fibroblasts [8]. A decrease in the ability of peripheral vessels to actively vasodilate positively correlates with the state of diastolic function of the right ventricle and the tone of pulmonary vessels necessary for normal gas exchange of lung tissue [2].

An imbalance between thrombotic, mitogenic, pro-inflammatory, vasoconstrictive factors and reverse action mechanisms - anticoagulant, antimitogenic, vasodilating, promotes vasoconstriction and thrombosis, proliferative and inflammatory changes in the pulmonary microvasculature [6].

Endothelin-1 (ET-1) is a peptide of endothelial origin that is characterized by potent vasoconstrictor and mitogenic properties on smooth muscle cells. ET-1 has a pro-inflammatory effect, activates neutrophils and mast cells, stimulates the production of cytokines, facilitating cell migration and promoting adhesion. ET-1 induces fibroblast proliferation, chemotaxis, and production of extracellular matrix components. In experimental studies in vitro, the mitogenic effects of ET-1 were shown upon activation of both types of receptors; type B receptors suppress the proliferation of SMCs in vivo [8, 9]. Endothelin type 1 binds to two types of receptors: type A (ETA), localized on smooth muscle cells and type B (ETV), localized on endothelial and smooth muscle cells. Activation of ETA and ETV receptors of smooth muscle cells causes vasoconstrictor and mitogenic effects. Due to the stimulation of ETV receptors, the clearance of ET-1 in the lungs increases, the production of nitric oxide and the release of prostacyclin increase. The question remains whether the increased ET-1 production is a cause or a consequence of LH. Activation of the endothelin system in patients with PH is the rationale for the use of endothelin receptor antagonists, blocking ETA receptors or simultaneously both types of receptors - ETA and ETV. For the treatment of PAH, two classes of ARE are used: one of them inhibits both types of ET receptors (double antagonists) - bosentan and macitentan belong to this class; others inhibit to a greater extent ETA receptors (selective antagonists) - these include ambrisentan [6].

Pharmacological effects of endothelin receptor antagonists. ARE, with constant use, cause regression of hypertrophy of the vascular wall and right ventricle, reduce inflammatory reactions and the collagen content in the lung tissue. Main effects: vasodilating and antiproliferative effects. It has also been shown in animal models of PAH that the effects are achieved equally with selective blockade of ETA receptors or blockade of both types of receptors. ET-1 is one of the most powerful and long-acting endogenous vasoconstrictors, 100 times higher than the effect of norepinephrine and 10 times the effect of angiotensin II [8].

ETA receptor blockade resulted in a 25% decrease in pulmonary vascular resistance. ETV receptor blockade had no effect on PVR. Clinical studies have not confirmed the hypothesis that treatment with selective AREs can be potentially more effective due to the preservation of the vasodilating effect and the implementation of ET-1 clearance through the activation of endothelial ETV receptors. Numerous studies show that the “selectivity phenomenon” is not characteristic of endothelin receptor antagonists; Macitentan, being a nonselective ARE, demonstrates high efficiency in the treatment of patients with PAH. Bosentan is the first non-selective ARE drug to block both types of receptors (ETA and ETV). In randomized trials in PH patients, the drug has demonstrated the ability to improve exercise tolerance, FC, hemodynamic and echocardiographic parameters, and to increase the time until clinical deterioration develops. Currently, the effectiveness of bosentan is shown in patients with IPH, PAH on the background of CTD, with Eisenmenger's syndrome in 5 randomized studies (pilot study 351, BREATHE-1, BREATHE-2, BREATHE-5, EARLY). Despite the effectiveness of bosentan in the treatment of patients with PH, a number of its side effects, such as changes in liver function parameters, erythema, make it difficult to use bosentan widely.

Ambrisentan is a selective type A endothelin receptor antagonist. The drug was studied in a pilot and two randomized trials ARIES-1 and ARIES-2. In patients with IPH, PH against the background of CTD and HIV infection, it was shown to be effective in the form of improved clinical symptoms, hemodynamic parameters, increased exercise tolerance, and lengthening of the time to the development of clinical deterioration. These effects persisted for at least 1 year of continuous therapy. Ambrisentan is recommended for the treatment of patients with PAH to improve exercise tolerance and slow the progression of clinical symptoms. In clinical studies, the effectiveness of the drug was established mainly in patients with IPH, inherited PAH, PAH due to CTD with FC II-III [5].

During treatment with ambrisentan, the following side reactions are observed: peripheral edema, fluid retention, headache, nausea, vomiting, diarrhea.

The efficacy analysis found that there was no significant statistically significant evidence of differences in clinical efficacy between ambrisentan and bosentan. At the same time, the best safety profile of the drug ambrisentan determined its advantage in terms of QALY (quality-adjusted life-year - years of life adjusted for quality, an indicator used in health economics that reflects the number of additional years of patient life obtained as a result of treatment, taking into account its quality during this period) in comparison with bosentan. Consistent with the findings of Kathryn Coyle et al. 2016, the QALY value when using the drug ambrisentan 5 mg (10 mg) and bosentan in the treatment of PAH II-II1 FC was 4.634 and 3.180 per 1 patient over 30 years; 3.904 and 2.960 respectively [7]. Macitentan is a new non-selective ET receptor antagonist characterized by

special physicochemical properties optimized to achieve high affinity for ET receptors in a lipophilic medium. These physicochemical properties of macitentan improve the drug's ability to penetrate into tissues [4].

The SERAPHIN study showed that therapy with the new ARE macitentan compared with placebo is statistically significant - 45% (at a dose of 10 mg) reduces the risk of disease progression and mortality; reduces the risk and frequency of hospitalizations associated with PAH and reduces the number of days spent in hospital. When using macitentan, compared with placebo, by the 6th month, the indicators of cardiac index, right atrial pressure, avPPA, PVR and NT-proBNP concentration significantly improved. Macitentan significantly improves clinically important outcomes, including 6-MTX and WHO FC. Macitentan is an effective first-line therapy for improving long-term outcomes in patients with both newly diagnosed PAH and previously diagnosed PAH [1].

Monotherapy with ambrisentan, bosentan and macitentan for the treatment of PAH patients with FC III and IV WHO has the highest recommendation class. Also effective is the combination of ARE with phosphodiesterase type 5 inhibitors (IFDE-5), with epoprostenol, selexipag and riociguat.

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