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TACTICS FEATURES OF CONDUCTING AND CHOOSING SPECIFIC THERAPY FOR ADULT PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION ASSOCIATED WITH CONGENITAL HEART DISEASE

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SUMMARY

PAH associated with CHD according to the Russian Register of Pulmonary Arterial Hypertension (PAH) and Chronic Thromboembolic Pulmonary Hypertension (CTEPH) is highly prevalent and ranks second after idiopathic pulmonary hypertension (IPH) in terms of prevalence among all forms of PAH and the first among associated forms. With the development of PAH, patients with congenital heart disease (CHD) require the appointment of a constant PAH-specific therapy. The article presents an overview of clinical trials of medications currently registered in the Russian Federation for this cohort of patients, including endothelin receptor antagonists (bosentan, macitentan, ambrisentan), phosphodiesterase type 5 inhibitors (sildenafil), soluble guanylate cyclase stimulants (riociguat) and prostacyclin analogues (iloprost).

Key words: *PAH associated with CHD; therapy of PAH associated with CHD; antagonists of endothelin receptors; bosentan; macitentan; ambrisentan; phosphodiesterase type 5 inhibitors; sildenafil; soluble guanylate cyclase stimulants; riociguat; analogs of prostacyclin; iloprost.*

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Pulmonary arterial hypertension associated with congenital heart disease (PAH-CHD) belongs to the 1st group in the classification of pulmonary hypertension (PH) (Table 1), which is characterized by the following criteria: increase in mean pulmonary artery pressure (mPAP) ≥25 mm Hg and pulmonary vascular resistance (PVR) >3 Wood units, normal pulmonary artery wedge pressure (PAWP) <15 mm Hg, normal or decreased cardiac output (CO), measured from right heart catheterization data at rest, and the absence of other causes for increased pulmonary artery pressure (left heart and lung disease, chronic pulmonary embolism of the pulmonary arteries, other rare forms with a mixed PH genesis) [1,2].

There are no precise epidemiological data on the prevalence of PAH-CHD. According to the European registers, the prevalence of PAH-CHD is 4-28% among patients with PAH, among them Eisenmenger syndrome is registered in 1-6% of patients [3].

PAH does not always accompany CHD. For example, the development of PAH can be expected only in 3% of patients with patent ductus arteriosus (PDA), in 10-17% of patients with atrial septal defect (ASD), in half of patients with ventricular septal defect (VSD), in 90% of cases in the presence of an atrioventricular septal defect and for all patients with a common arterial trunk [3].

At the same time, CHD is the most common cause of the PAH development in our country. According to the Russian registry of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension, the proportion of adult patients with PAH-CHD is 34% and is the second most common among all forms of PAH and the first among associated forms [4].

Table 1. Structure of pulmonary arterial hypertension in clinical recommendations

Group 1: Pulmonary arterial hypertension	1. Idiopathic 2. Heritable 3. Drug and toxin induced 4. Associated with: Connective tissue disease HIV infection Portal hypertension Congenital heart disease Schistosomiasis

The clinical classification of systemic-to-pulmonary shunts associated with PAH is presented in Table 2, including Eisenmenger syndrome, PAH associated with predominance of systemic-to-pulmonary blood shunting, PAH with small / coincidental defects, and residual PAH.

As a rule, patients with CHD in the presence of PAH are already inoperable. The only group of patients who can undergo surgical or endovascular correction are patients with PAH associated with predominant systemic-to-pulmonary blood shunting in the presence of medium and large defects, in which the pulmonary vascular resistance (PVR) is moderately elevated. The operative intervention is justified with PVR <2.3 Wood units and is contraindicated with PVR >4.6 Wood units; at intermediate values can be determined additionally, based on the experience of the surgical center (Table 3) [1]. For patients with Eisenmenger syndrome, surgical intervention is contraindicated, since the removal of a functioning shunt will inevitably lead to an overload of the right heart, right ventricular heart failure and death of the patient. For patients with PAH associated with small defects (VSD <1 cm and ASD <2 cm), surgical correction is ineffective and therefore experts are not recommended, but for patients with residual PAH is not discussed. Thus, virtually all patients with PAH-CHD need the appointment of permanent medical treatment.

The basis of medical therapy is the so-called PAH-specific therapy. For the treatment of patients with PAH-CHD can be used medications that affect the most studied at the present three pathways in PAH pathogenesis. Medications affecting the level of endothelin (bosentan, ambrisentan and macitentan), nitric oxide (NO) (sildenafil and riociguat) and activating prostanoid receptors (inhaled iloprost) are registered in Russian Federation.

Most randomized clinical trials (RCTs) have been performed for patients with Eisenmenger syndrome. Patients with small defects and residual PAH were included in many RCTs conducted for patients with PAH. The use of PAH-specific therapy is practically not studied only for patients with large defects and preferential shunting of the blood at rest from left to right. This is due to the fact that, in the first place, a number of such patients can still perform a surgical correction of the blemish, and secondly, with the appointment of a pathogenetic medication there is a potential opportunity to increase the volume of blood entering the pulmonary artery, thereby activating a cascade of pathological reactions involving endothelial dysfunction, proliferation, procoagulant reactions, and so on, which can worsen the situation.

Table 3. Recommendations for the correction of congenital malformations with the predominant systemic-to-pulmonary direction of blood shunting

PVR (Wood)	PVR Index (Wood x m^2)	Indication	Class and strength of recommendations
< 2,3	<4	Yes	IIa C
> 4,6	>8	No	IIa C
2,3 – 4,6	4-8	At center discretion	IIa C

Currently, the largest evidence base in this category of patients has bosentan following a multicentre, double-blind, randomized, placebo-controlled study BREATHE-5 (Bosentan Randomized trial of Endothelin Antagonist THErapy-5) [5]. Bosentan is a non-selective endothelin receptor antagonist (ERA) blocking both receptor types (ETA and ETB). The study included 54 patients with Eisenmenger syndrome of the WHO functional class III (FC), of which 67% had PAH due to ASD, 24% due to VSD and 9% combination of ASD + VSD. Patients were randomized 2:1 to receive bosentan at an initial dose of 62.5 mg twice daily for 4 weeks, followed by a dose increase of 125 mg twice daily and placebo. By the 16th week of treatment, bosentan demonstrated a decrease in PVR (-472 dyn·s·cm^5, p = 0.038), mean pulmonary artery pressure (mPAP) (-5.5 mmHg, p = 0.036) and an increase in exercise tolerance: the distance in 6-minute walking test (6MWD) increased by 53.1 m, p = 0.0079. 35% of patients in the active treatment group compared with 13% of the placebo group improved FC to II, and only 3% compared to 6% of patients reported worsening of FC to IV. In this case, therapy with bosentan did not worsen the saturation of the blood with oxygen and was characterized by good tolerability.

37 patients continued to follow the open phase until 24 weeks of therapy. In the group receiving a placebo earlier, an increase in 6MWD was recorded at 33.2±23.9 m; in the group previously receiving active therapy, the incremental gain was 6.7±10.0 m, in total for the entire observation period 61.3±8.1 m. At the end of the study, 64.9% of patients had FC II and 35.1% remained in FC III.

The results of the BREATHE-5 study allowed us to recommend bosentan for the treatment of patients with Eisenmenger syndrome of WHO FC III with class and level of evidence base IB [1,2].

Patients with PAH-CHD, including 17% with Eisenmenger syndrome, FC II were included in the EARLY study along with patients of another etiology of PAH. After 24 weeks of therapy, a

Table 2. Clinical classification of congenital systemic-to-pulmonary shunts associated with PAH

I	Eisenmenger syndrome	Patients with large intra- and out-of-cardiac defects, who, due to the progression of the disease, had an increase in PVR, which led to the formation of a bi-directional flow or right-handed blood shunting. They are characterized by the presence of central cyanosis, secondary erythrocytosis and multiple organ failure.
II	PAH associated with predominance of systemic-to-pulmonary blood shunting	It includes medium and large defects, in which the PVR is moderately elevated, mainly the systemic-to-pulmonary blood flow remains. At rest there is no cyanosis.
III	PAH with small/coincidental defects	Increase in PVR in the presence of small defects are detected (usually defects of IVC <1 cm and defects of IAC <2 cm, measured by ECHO), which alone do not explain the increase in PVR. The clinical picture is similar to IPH.
IV	PAH after the surgical correction	Correction of CHD was performed, but PAH is recorded immediately after surgery or appears after months/years in the absence of significant postoperative residual lesions or birth defects

Table 4. Effects of switching patients with PAH-CHD from bosentan therapy to macitentan

Factors determining the forecast	Bosentan	Macitentan	p
Hospitalization due to heart failure *,%	7,5	2,5	0,50
Syncope condition,%	2,5	2,5	1,00
WHO FC III - IV, %	48	23	0,004
6MWD, m±SD	394±125	397±123	0,79
SaO2, %, IQD	87 [81-93]	85 [81-94]	0,42
Ferritin, ng/l, IQD	45 [22-89]	63 [28-110]	0,41
NT-proBNP, ng/l, IQD	723 [311-1328]	488 [215-1291]	0,02
TAPSE, mm±SD	19±4	21±5	0,002

Notes: IQD – Interquartile distance; SD – standard deviation; TAPSE – tricuspid annulus plane systolic excursion

significant decrease in PVR was recorded (-22.6%, p<0.0001), an increase in 6MWD +19.1 m was noted, which was insufficient to achieve statistical significance [6].

At the end of 2015, a new nonselective antagonist of endothelin receptors, macitentan, was registered in the Russian Federation for the treatment of patients with PAH WHO FC II - III, including for patients with a corrected simple congenital heart disease (PAH-CHD). The creation of macitentan was the result of an intensive research for new medications, in which more than 2500 molecules were synthesized and investigated for activity, efficacy and safety profile. The main task was to find a molecule with a higher efficacy in PAH, as well as a favorable safety profile and tolerability, with minimal risks of development of adverse events, especially with regard to hepatic enzyme activity.

Macitentan, in comparison with other representatives of the ERA class, has optimized physicochemical properties, which favor tissue penetration. In the experiment it was shown that the tissue-targeting potential of macitentan is 600 times greater than that of ambrisentan and 60 times higher than of bosentan [7]. Macitentan demonstrated longer receptor occupancy time (t1/2) which is 15 times greater than of ambrisentan and bosentan and allows reducing the frequency of administration up to 1 time per day [8]. Macitentan remains highly active at elevated ET-1 concentrations, in contrast to ambrisentan and bosentan [8], which is extremely relevant for PAH.

The positive effects of macitentan were shown in a large, multicenter, double-blind, placebo-controlled study SERAPHIN, aimed at assessing morbidity and mortality of patients with PAH [9]. The study included 742 patients, of whom 8.7% were patients with residual PAH after surgical correction of simple defects (ASD, VSD, PDA). The average age was 46.6±16.3 years; 52.5% had FC I-II, 47.5% FC III-IV. Patients were randomized into 1:1:1 groups and received 3 mg or 10 mg of macitentan or placebo once per day. Moreover, more than half of the patients (63.7%) included in the study were on stable PAH-specific therapy for at least 3 months prior to randomization by phosphodiesterase type 5 inhibitors (61.4%), oral / inhaled prostanoids (5,4%), calcium channel blockers or L-arginine.

The primary endpoint was the time until the onset of the first event, including death from all causes or atrial septostomy, or pulmonary transplantation, or the need for administration of intravenous / subcutaneous therapy with prostanoids or other worsening of PAH (worsening of FC or right ventricular decompensation + decrease in 6MWD > 15% + need for escalation therapy - addition of another PAH – specific drug or parenteral diuretics).

As a result of the study, the ability of macitentan at a dose of 10 mg per day to reduce the risk of morbidity and mortality events by 45% was shown. Macitentan in monotherapy significantly reduced the risk of a morbidity or mortality event by 55% in the 10 mg and by 38% when it was prescribed as the second drug. A 49.8% reduction in the incidence of PAH-related hospitalization and a 52.3% reduction in the number of hospitalization days were reported. When assessing secondary endpoints by the 6th month of therapy, an increase in 6MWD was found to be 22.8m (p = 0.007), with a more significant distance increase for patients with FC III-IV (+37 m), with FC I-II (+12,3m). Improvement of FC was detected in 22% of patients (p = 0.006). When evaluating hemodynamic parameters compared to the placebo group, macitentan significantly reduced the PVR and increased the cardiac index (CI): the therapeutic effect corrected for placebo was 61.5% (97.5% CI: 51.0, 74.3) and 0, 63 (97.5% CI: 0.28, 0.97), respectively.

Macitentan has an optimal safety profile. Thus, when prescripted at a dose of 10 mg per day, the incidence of peripheral edema was comparable to the placebo group (44% vs 45%, respectively), more than 3 times the upper limit of normal (x UNL) of liver transaminase was registered less frequently than in placebo group (3.6% vs. 4.5%, respectively), slightly more often >3 UNL of hepatic transaminase in combination with >2 UNL of bilirubin (2.1% vs. 1.7%, respectively) was detected. The appearance of anemia was the only criteria registered more often during the treatment by macitentan (13,2% vs 3,2% with placebo), but for patients with PAH-CHD significant increase in hemoglobin and erythrocyte is characteristic, and this side effect is not yet clinically evaluated.

At present, the first results have already appeared of switching stable bosentan therapy for macitentan [10]. So in a multicentre prospective cohort study, 40 patients with PAH-CHD (Eisenmenger syndrome 75%, with systemic-to-pulmonary shunts 7.5%, with minor defects 2.5% and with residual PAH 15%) were included [11]. These patients had previously received bosentan for a long time (the median duration was 7.2 years). The replacement of bosentan with macitentan was performed after 24 hours withdrawal. After 6 months of therapy with macitentan, a significant reduction in the percentage of severe patients with FC III-IV (23% vs 48% baseline, p = 0.004), a decrease in NT-proBNP from 723 (311-1328) to 488 (215-1291) (p = 0.02), tricuspid annular plane systolic excursion (TAPSE) increased (21±5 vs 19±4 mm, p = 0.002) (tab 4). In the study, 40% of patients had Down's syndrome, which probably could influence overall 6MWD levels. After switching to macitentan, no serious adverse events were noted. One death was reported due to sepsis.

Another prospective, open-label study Herbert S et al. (2017) [12] included 15 adult patients with PAH at the age of 38 (23-61)

years, 46.7% of whom were women, and 8 patients with Down syndrome. 8 patients had complex CHD, which is rare in clinical studies. 9 patients had previously received bosentan, including 6 in combination with the PDE5 inhibitors, 2 patients received monotherapy with PDE5 inhibitors and 4 had not previously been treated. The median of the therapy period with macitentan was 289 (0-694) days. The study showed a significant 6MWD increased from 286 (120-146) to 360 (150-450) meters (p<0.05) despite a large number of included patients with Down syndrome. Medians of FC, oxygen saturations (SaO2) at rest and after exercise, Borg Dyspnoea Index, TAPSE tended to improve, but did not gain statistical significance.

Switching to macitentan of adult patients with PAH-CHD in most cases was well tolerated, with satisfactory oxygen saturation and encouraging results of efficacy evaluation. There were no violations of functional liver samples or a decrease in hemoglobin level. One lethal outcome was recorded after 10 days of treatment of patient FC IV with oxygen saturation of 67%; 2 patients were excluded: 1 case due to a side effect (rash), the second because of non-compliance with the treatment regimen due to learning problems with Down's syndrome.

Unfortunately, a large (n=226) multicenter, double-blind, randomized, placebo-controlled study MAESTRO (MAcitentan in Eisenmenger Syndrome To Restore exercise capacity), launched in 2013, ended prematurely in August 2016 due to the lack of reliable positive dynamics in the 6MWD estimate background of ongoing therapy with macitentan 10 mg per day versus placebo for patients with PAH. A 20% reduction in the level of NT-proBNP (p = 0.006), a decrease in the PVR index of - 409.8 dyne*s/cm^5/m^2 was shown compared to + 79.4 dyne*s/cm^5/m^2 in placebo (p=0.018) [13].

If we draw a parallel with the results of the BREATHE-5 and EARLY studies, then the design flaws of the MAESTRO study become obvious. It included 59.7% of patients with FC II, at the same time in BREATHE-5 all patients were FC III. In the EARLY study, in which only patients with FC II participated, the statistical significance of the dynamics in 6MWD also failed to reach statistical significance. In addition, the MAESTRO study allowed the inclusion of patients receiving drugs from the group of PDE5 inhibitors (27.4%).

Thus, by analyzing the results of the MAESTRO study, it can be concluded that obviously lighter patients were included, and given the low rate of progression of the disease of patients with PAH, some of whom have already received treatment, it probably takes a longer period than 16 weeks observation.

Another representative of the ERA class ambrisentan is selective for endothelin type A receptors. In an open prospective single-center placebo-uncontrolled for 17 patients with Eisenmenger syndrome after 163±57 days a significant improvement in 6MWD was revealed from 389±74 to 417±77 meters (p = 0.03), 2 patients out of 15 improved FC. There was no significant adverse effect of ambrisentan therapy on hemoglobin levels (p = 0.11) and SaO2 (p = 0.75) [14]. In long-term follow-up (up to 2.5±0.5 years), when compared with baseline and short-term results, the stability of SaO2, hemoglobin and FC was noted.

To influence the deficiency of NO, phosphodiesterase type 5 inhibitors (PDE5 inhibitors) and stimulants of soluble guanylate cyclase are currently used. The former blocks PDE-5, decreasing the disintegration of cyclic guanosine monophosphate (cGMP). There were no large placebo-controlled RCTs with PDE5 inhibitors for patients with PAH-CHD. The only double-blind, placebo-controlled 12-week trial of the use of sildenafil for patients with PAH is SUPER-1 (Sildenafil Use in Pulmonary Arterial Hypertension), including 7% of patients with residual PAH. According to the results of therapy, a significant increase in 6MWD (p<0.0001), cardiac output (p<0.05), decrease in PVR (p, 0.0001) and mPAP (p <0.05) was shown. At the same time, subanalysis was not performed for patients with CHD [15].

Results of some placebo-uncontrolled works were published, the largest of which are works from China. In the first, 60 patients were included in the open multicenter study, including 48 with Eisenmenger syndrome, 4 with residual PAH, 8 with other CHD. After 12 weeks of sildenafil 75 mg per day, there was a significant improvement in 6MWD (+50.95 m [42-69], p <0.0001), a decrease in Borg dyspnoea (-0.47 points, p = 0.03), mPAP (-6.42±13.36 mm Hg, p = 0.0002), PVR (-518.28±759.05 dyne*s/cm^5/m^2, p <0.0001) and increase in CI (+ 1.09±4.38 l/min/m2, p <0.0001). A total 43.34% of patients improved their FC: 21.67% (initially not one patient), FC increased to I, the number of patients with III FC decreased from 22% to 10% and IV FC (none vs. 3%) [16].

The second open multicenter study was longer. It included 84 patients with Eisenmenger syndrome FC II-III. After 12 months of sildenafil 60 mg per day, a significant increase in 6MWD (+ 56m [42-69], p <0.0001), SaO2 (2.4%, p<0.0001), a decrease in mPAP(-4, 7 (-7.9, -1.5) mm Hg, p<0.001), the PVR index (-774 (-314; -634) dyne*s/cm^5/m^2, p<0.0001) were detected [17].

Riociguat is the representative of a new class of medications - a stimulant of soluble guanylate cyclase (sGC). Riociguat is able to increase biosynthesis of cGMP in two ways: by direct stimulation of the sGC like NO, and by increasing the sensitivity of cGMP in conditions of low concentrations of endogenous NO, which distinguishes it from sildenafil.

Riociguat was studied in a 12-week randomized, double-blind, placebo-controlled study PATENT for patients with PAH. Subsequently, a subanalysis was performed for patients with PAH-CHD (18). 35 patients with residual PH after correction of CHD (ASD 40%, VSD 34%, OAD 23%, other defects 3%) were assigned riociguat according to a scheme with a titration dose of 1.5 to 2.5 mg 3 times per day. A significant reduction in the level of NT-proBNP (-164±317, placebo -46±697 pg/ml), PVR (-250±410, placebo -66±632 dyne*s/cm^5/m^2) was shown, 6MWD (+ 39±60; placebo 0±42 m) and improvement in FC (21/79/0% vs 8/83/8% in placebo for II/III/IV, respectively). However, despite these data, the idiopathic PH, heritable PAH and PAH associated with systemic connective tissue diseases are currently represented among the forms of PAH in the instruction for use.

Among the analogs of prostacyclin, only iloprost for inhalation has been registered in the Russian Federation. Twelve patients with Eisenmenger syndrome (ASD – 4, VSD – 5, ASD + VSD – 2, OAD – 1), 75% of whom had FC III and 25% IV, were prescribed iloprost at a dose of 60 μg per day. After an average of 18.6±7.4 months, a significant increase in 6MWD (349.4±134.7 compared with 255.8±120.4 initially, p = 0.013), SaO2 (84.9±13, 0 vs. 80.6±14.2, p = 0.04), 10 patients improved the FC by at least 1 (p = 0.007). There were no significant changes in the size of the right ventricle and mPAP according to ECHO. The therapy was well tolerated, there was no refusal of treatment, side effects most often met mild headache and shortness of breath. No deaths were recorded, despite the fact that they were quite severe patients. In the iloprost instruction for use, there is also no indication for PAH-CHD.

Despite the potential attractiveness, the results of studies on the benefits of combined PAH-specific therapy using classes of PAH drugs that affect different pathogenesis pathways are controversial. Some studies have shown that adding sildenafil to bosentan or bosentan for epoprostenol can improve hemodynamic performance and exercise tolerance [19, 20]; others have shown

no benefit from this combination [21]. At present, there are no data from large long-term RCTs on the use of combination therapy in this cohort of patients.

Thus, taking into account the RCTs conducted, the following recommendations on the conducting of PAH-specific therapy are currently formulated [1]:

1. ERA bosentan is indicated for patients with Eisenmenger syndrome with WHO FC III (I B)

2. Other AREs, PDE5 inhibitors and prostanoids should be considered for patients with Eisenmenger syndrome (IIa C)

3. Combination therapy may be considered for patients with Eisenmenger syndrome (IIb C)

4. Patients with Eisenmenger syndrome are not recommended to use calcium antagonists (III C)

As for the recommendations on the use of PAH-specific therapy with other groups of systemic-to-pulmonary shunts, it is hoped that in the near future experts will analyze all the experience of RCTs and registers, which will allow to develop recommendations for this category of patients.

In general, patients with PAH-CHD differ from other forms of PAH with a more favorable prognosis, and adherence to recommendations for diagnosis and treatment contributes to better survival. Current estimated survival rates are 87% (77-93%) and 86% (60-96%) for 20 years from the date of diagnosis for Eisenmenger syndrome and systemic-to-pulmonary shunts, respectively; somewhat worse for PAH associated with small defects (66% (16-91%) over 15 years). Patients in whom PAH persists or developed after surgical correction have the worst prognosis: a survival rate of 36% (12-72%) for 20 years of follow-up [22]. The low survival rate of the latter group dictates, on the one hand, the need for a balanced approach to the selection of surgical treatment tactics, and on the other hand, the rational choice of drug-specific therapy.

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