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CASE REPORT ON THE SUCCESSFUL USE OF A NEW SELECTIVE PROSTACYCLIN IP RECEPTOR AGONIST, SELEXIPAG, IN A PATIENT WITH IDIOPATHIC PULMONARY HYPERTENSION

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SUMMARY

Idiopathic pulmonary arterial hypertension (IPAH) is a rather rare cardiovascular disease of unknown origin and, at the same time, the most common form of pulmonary arterial hypertension (PAH). It is characterized by increased mean pulmonary artery pressure of ≥ 25 mm Hg and increased pulmonary vascular resistance of > 3 Wood units. One of the key components of IPH pathogenesis is the disorder in the prostacyclin pathway leading to hypertrophy of the smooth muscle and endothelial cells, fibrotic changes, inflammatory response and vasoconstriction, which results in small artery and arteriole remodeling. For severe cases of PAH, in Russia only used one drug acting on the prostacyclin pathway, i.e., iloprost for inhalation. However, this therapy has a number of restrictions on the use. Selexipag is the first selective oral prostacyclin IP-receptor agonist intended for the treatment of patients with PAH. The efficacy and safety of Selexipag in patients with PAH were investigated in GRIPHON study, the largest-scale clinical trial ever conducted in patients with pulmonary hypertension. The publication presents a case of successful use of Selexipag as a part of the combination therapy in a patient with IPAH.

Keywords: *idiopathic pulmonary arterial hypertension, pulmonary arterial hypertension, Selexipag.*

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Pulmonary arterial hypertension (PAH) is a rare disease associated with the pulmonary circulation artery remodeling and increased pulmonary vascular resistance (PVR), which causes right ventricular failure and premature death of the patients. The early diagnosis of PAH and timely prescription of PAH pathogenetic therapy represents a substantial problem both in Russia and abroad. However, the recent decades have seen a substantial progress in the study of PAH pathophysiologic mechanisms, which has made it possible to put a number of PAH-specific drugs acting on the key components of PAH pathogenesis into clinical practice: endothelin receptor antagonists (ERA), phosphodiesterase type 5 inhibitors (PDE5 inhibitors), soluble guanylate cyclase stimulators and prostanoids. Despite the achieved success in PAH therapy, it is still an incurable disease, and the survival rates still give rise to concern and have to be improved [1,2].

During the last years, new generation of PAH-specific drugs, such as riociguat and macitentan, have been put into clinical practice [3,4], however, parenteral prostanoids used in the most severe cases are unavailable in the Russian Federation up to the present day.

Considering the share of severe cases – of functional classes III–IV (WHO) – and thus the increased need for combination therapy prescription, it remains relevant to extend the range of PAH-specific drugs, including the group of prostanoids that is currently only represented by iloprost for inhalation in the Russian Federation.

Selexipag is the first selective oral prostacyclin IP-receptor agonist intended for the treatment of patients with PAH. The efficacy and safety of Selexipag in patients with PAH was investigated in the GRIPHON study, the largest-scale clinical trial ever conducted in patients with pulmonary hypertension. GRIPHON was a phase III long-term, multi-center, randomized, placebo-controlled, event-driven study conducted in parallel groups, which enrolled of 1,156 patients with PAH who received treatment in 181 healthcare centers in 39 countries, including Russia [5]. The composite primary endpoint of the study was set as a period from randomization to disease progression (hospitalization for worsening of PAH, or initiation of treatment with parenteral prostanoids, or long-term oxygen therapy, or the need for lung transplantation, or balloon atrial septostomy), or death, until the end of the treatment period.

The following case is provided as an example to demonstrate the efficacy and safety of the use of Selexipag in patients with PAH, as well as the possibility of optimizing the medical therapy.

The patient D. of 24 years old has been observed for a long time in the Pulmonary Hypertension and Heart Disease Department of the Clinical Cardiology Institute named after A.L. Myasnikov, with the diagnosis of idiopathic pulmonary arterial hypertension (IPAH).

According to the medical history, the patient first experienced shortness of breath at the age of 14, however, the patient did not consult a doctor then. At the age of 16, the patient first experienced syncopal conditions at the peak loads. The diagnosis of vegetovascular dystonia was set for the patient. And after as long as 4 years, the patient was sent to a cardiologist. Based on echocardiography (Echo-CG) data, signs of pulmonary hypertension have been detected for the first time, with the pulmonary artery systolic pressure (PAPs) of 95 mm Hg. No right heart catheterization (RHC) has been conducted. The diagnosis of IPAH was set. Diltiazem, 90 mg per day, was prescribed. During 4.5 years of the therapy, gradual worsening of the patient's condition and a reduction in exercise tolerance was observed. Therefore, the local healthcare facility professionals supplemented the therapy with Bosentan, 125 mg, twice daily. After a year, in 2010 the patient was for the first time admitted to the National Medical Research Center of Cardiology, with systemic circulation decompensation and syncopal conditions at peak loads.

Based on physical examination data, the patient's condition as of the time of admission was assessed as moderately severe. The skin was clean, of physiologic coloration, no lymph nodes were palpable, no visible pathology of the osteoarticular and muscular systems was observed. Shin and foot edema was observed. The chest shape was normosthenic, both of the hemithoraxes uniformly participated in respiratory movements, the chest was painless on palpation, and clear percussion sound was heard. Vesicular respiration was heard above the lungs, and no wheezes were heard. No expansion of the borders of relative heart dullness was revealed in the course of the circulation organs examination. During auscultation of the heart, loud second heart sound was heard above the pulmonary artery (P2), and the systolic murmur was noted above the tricuspid valve. The cardiac rhythm was regular, with the heartbeat rate of 71 beats per minute; blood pressure 110/70 mm Hg. No pathologic changes were detected as a result of examination of the digestive and the urinary system. No impairment of the neuropsychological status or sensory function was revealed. According to the laboratory test data, increase in N-terminal pro-brain natriuretic peptide (NT-proBNP) up to 1,850 ng/ml was observed, with no other substantial deviations from the normal values (Tables 1, 2).

In a 6-minute walking distance (6MWD), the distance covered was 379 m, and the shortness of breath was assessed as 3 points of Borg scale. Electrocardiogram (ECG): sinus rhythm with the heartbeat rate of 72 beats per minute; right axis deviation, p-pulmonale type change in the atrial wave, sings of right ventricular hypertrophy. Incomplete right bundle branch block (Fig. 1).

In the Echo-CG, right heart enlargement was observed, with associated LV size reduction (Table 3) as well as the pulmonary trunk enlargement up to 3.1 cm. Moreover, 2nd degree tricuspid regurgitation, PASP 75 mm Hg; and sings of increased central venous pressure, i.e., enlarged inferior vena capa and its insufficient collapse during expiration, were observed. In the X-ray examination of chest organs, changes corresponding to high-degree arterial pulmonary hypertension, i.e., Moor index increase to 38%, Lupi index increase to 40%, were observed. Enlargement of the lung roots (right root breadth of 16 mm); cardio-thoracic index = 57%.

Thus, based on the complete examination data, including RHC (Table 4), the diagnosis of IPAH was confirmed.

Considering the failure to achieve the therapy goals (Fig. 2), we obviously had to choose PAH-specific therapy escalation.

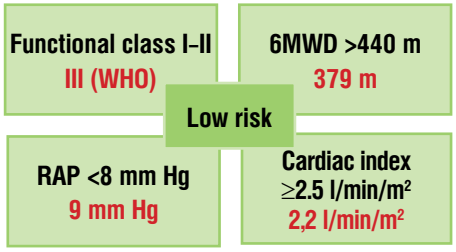

Figure 2. Absence of therapy goals in the patient D

TABLE 1. BIOCHEMICAL BLOOD TEST RESULTS

Test	Result	Normal values	Unit of measurement
Creatinine	93	44,0 - 106,0	μmol/l
Glucose	4,26	3,50 - 5,80	mmol/l
Triglycerides	1,66	0,50 - 2,30	mmol/l
Potassium	4,5	3,5 - 5,3	mmol/l
Sodium	145,6	138,0 - 153,0	mmol/l
Chlorine	102,2	98,0 - 108,0	mmol/l
Total protein	79,5	64,0 - 83,0	g/l
Total bilirubin	30,7	1,7 - 20,5	μmol/l
AST	35	3,0 - 29,0	Unit/l
ALT	37	3,0 - 40,0	Unit/l
Cholesterol	4,5	3,50 - 5,20	mmol/l
HDL cholesterol	0,95	0,90 - 1,89	mmol/l
LDL cholesterol	2,80	0,08 - 4,00	mmol/l
NT-proBNP	1850	0,0 - 150,0	pg/ml
D-dimer	200	До 500	ng/ml

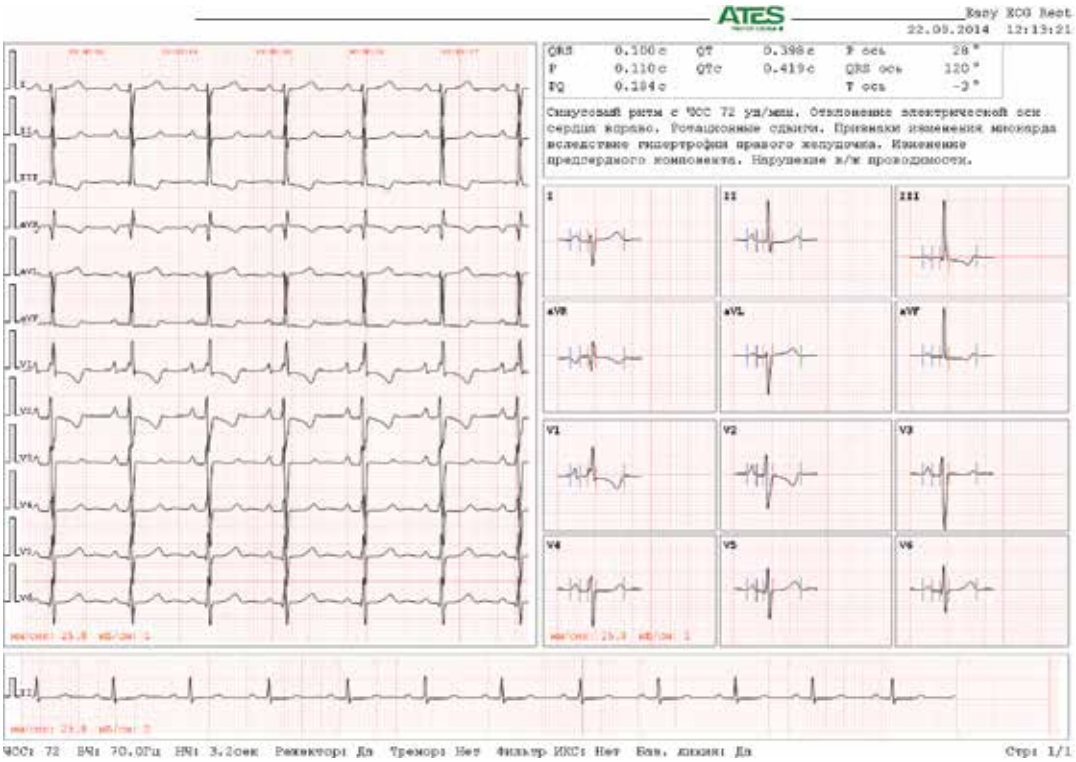

Figure 1. Electrocardiogram of the patient D

At that time, the National Medical Research Center of Cardiology was included in GRIPHON study. The patient was scanned and randomized into the study.

The patient received selexipag 1,200 μg, twice daily. The principal factor limiting further dose titration was headache that required constant analgesic intake.

Thus, the following therapy was prescribed to the patient: Bosentan 125 mg, twice daily; Selexipag 2400 μg per day; Ivabradine 10 mg per day; Torasemide 7.5 mg; Spironolactone 50 mg. Diltiazem was withdrawn because of the hypotension tendency.

In response to the therapy, the patient's condition has improved, and stable clinical effect is confirmed by both RHC (Table 4), Echo-CG (Table 5) data, and by assessment of the patient's functional status (Fig. 3). All therapy goals and also a low 1 year mortality risk have been achieved in the patient (Table 6).

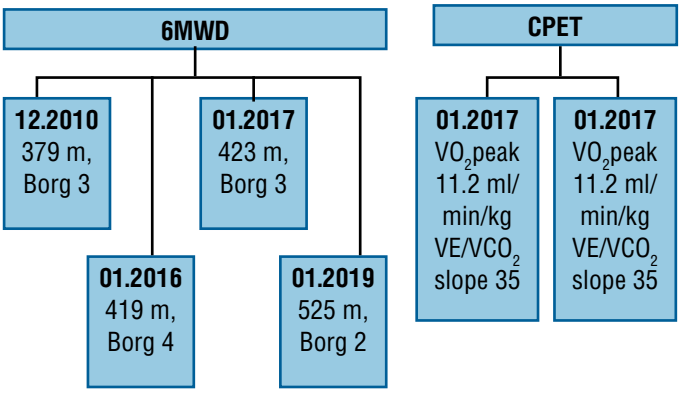

Figure 3. Functional status changes

TABLE 2. CLINICAL BLOOD TEST RESULTS

Test	Result	Normal values	Unit of measurement
Basophils	0,06	0,00 - 0,20	thous./μl
Hematocrit	33	37,0 - 47,0	%
Hemoglobin	12,92	12,00 - 16,00	g/dl
RBC anisotropy factor	13,5	11,5 - 14,5	%
Leukocytes	7,9	4,8 - 10,8	10*9/l
Lymphocytes	1,8	0,9 - 5,2	thous./μl
Monocytes	0,35	0,20 - 1,00	thous./μl
Neutrophils	5,9	1,9 - 8,0	thous./μl
Mean corpuscular hemoglobin concentration	33	33 - 37	g/dl
Mean cell hemoglobin	28,3	27,0 - 31,0	pg
Mean corpuscular volume	82,8	81,0 - 99,0	fl
Thrombocrit	0,17	0,02 - 1,00	%
Platelets	201	130 - 400	10*9/l
Eosinophils	0,24	0,00 - 0,80	thous./μl
Erythrocytes	4,69	4,20 - 5,40	10*12/l
ESR	10,0	0,0 - 20,0	mm/h

TABLE 3. ECHOCARDIOGRAPHY DATA AS AT THE TIME OF ADMISSION OF PATIENT D

Parameters	December 2010	N
AO, cm	3.1	2.0–3.7
LA, cm	3.0	2.0–4.0
LV EDD, cm	3.5	4.0–5.5
EF, %	60	>60
LV PWT, cm	1.0	0.7–1.1
IVST, cm	1.0	0.7–1.1
diastolic LV eccentricity index	1,26	1
RA area, cm^2	20	≤18
RV anterior-posterior dimension, cm	3.3	<3.0
RV anterior wall thickness, cm	0.7	≤0.5
TAPSE, cm	1,37	>1,6
FAC RV, %	20,3	>35%
RV EF (3D), %	29,4	>44%
PASP, mm Hg	75	<36
WP, mm Hg	6	
PA trunk, cm	3.1	<2.5
IVC	2.2/1.5 collapse <50%	
Tricuspid insufficiency	2	1

DISCUSSION

The therapy acting on the key components of the pathogenesis is an important achievement in the current medication approaches to PAH. The strategy of treating IPH patients is oriented towards achievement of the therapy goals defined as a low mortality risk, which includes: arrival at I or II functional class according to the classification of World Health Organization, normalization of the dimensions of the right heart compartments and of the right ventricle (RV) function as determined by echocardiography data and/or magnetic resonance tomography data (right atrium area (RA) <18 cm^2, no pericardial effusion), reduction in the mean right atrial pressure (MRAP) <8 mm Hg and increase in the cardiac index (CI) ≥2.5 l/min/m^2, distance in the 6-minute walk test of over 440 meters, peak oxygen consumption (VO_2peak) >15 ml/min/kg and carbon dioxide ventilation equivalent (VE/VCO_2 slope) <36 l/min as determined by the Cardiopulmonary test (CPET) data, normal values of NT-proBNP, etc. The risk of 1 year mortality is determined in PAH patients by assessing all the foregoing factors [2, 6]. For severe cases of PAH, the Russian doctors have only one drug acting on the prostacyclin pathway, i.e., iloprost for inhalation. However, this therapy has a number of restrictions on the use. The inhalation form of iloprost is characterized by the half-life of 5–25 minutes, therefore 6 to 9 daily inhalation sessions are required, depending on the patient's individual need and tolerability. Depending on the applicable product dose, the inhalation session duration is about 4 to 10 min. It is necessary to use a new Iloprost ampoule for each inhalation. The entire ampoule content is to be transferred to the nebulizer chamber immediately before use. It is necessary to strictly observe hygiene and inhalator cleaning instructions. The solution that has not been spent for inhalation is not suitable for further use. The inhalation administration of Iloprost is frequently accompanied by such local adverse reaction as coughing, which restricts the use of the drug. The inhalation of Iloprost may also increase the risk of bronchial spasm development [7].

Selexipag is the first oral selective prostacyclin receptor (IP) agonist. In 2015, the results of a III phase international, double-blind, placebo controlled clinical study involving parallel groups randomized in a ratio of 1:1 (GRIPHON) were presented. The principal objective of the study was to assess the long-term efficacy and safety of Selexipag in patients with PAH. According to clinical outcome assessment of 1,156 PAH patients as part of the GRIPHON study, Selexipag used either as a single agent or in combination with endothelin receptor agonists and/or phosphodiesterase type 5 inhibitors (PDE5 inhibitors) provided

TABLE 4. RHC PARAMETER TRENDS

Parameters	December 2010	January 2016	January 2017	February 2019	N
PAPs /PAPd/ PAPm, mm Hg	73/28/44	85/30/47	80/26/42	78/25/39	<25 (срДЛА)
mRAP, mm Hg	9	8	6	6	2–6
PAWP, mm Hg	1	1	7	9	1–15
CO, l/min	3.9	4.6	4.6	4.8	4.0–8.0
CI, l/min/m^2	2.2	2.6	2.7	2.8	2,5-4,0
SvO_2, %	61	60	58	67	60-80
PVR, dyne•s•cm^{-5}	790	782	678	500	<240

TABLE 5. ECHOCARDIOGRAPHIC PARAMETER TRENDS

Parameters	September 2010	January 2016	January 2017	February 2019	Normal values
AO, cm	3.1	3.3	3.2	3.2	2.0–3.7
LA, cm	3.0	3.3	3.3	3.4	2.0–4.0
LV EDD, cm	35	4.1	4.2	4.2	4.0–5.5
EF, %	60	60	60	60	>60
IVST, cm	1.0	1.0	1.0	1.0	0.7–1.1
LV PWT, cm	1.0	1.0	1.0	1.0	0.7–1.1
diastolic LV eccentricity index	1.26	1.2	1.2	1.16	1
RA area, cm^2	20	20	20	17.5	≤18
RV anterior-posterior dimension, cm	3.3	3.4	3.2	2.7	<3.0
RV anterior wall thickness, cm	0.7	0.6	0.6	0.55	≤0.5
TAPSE, mm	1.37	1.7	1.7	1.9	>1,6
FAC RV, %	20.3	23	23	28	>35%
PASP, mm Hg	75	89	70	73	<36
PA trunk, cm	3.1	3.2	3.2	3.0	<2.5
IVC, cm	2.2/1.5 collapse <50%	2.1/1.5 collapse <50%	2.0/0.7 collapse >50%	2.1/1.0 collapse >50%	Up to 2.2 coll. >50%
TR degree	2	1–2	1-2	1–2	1
Pericardial effusion	-	-	-	-	-

the 40% reduction in the risk of death or a complication related to PAH s (composite primary endpoint: death from any causes, hospitalization for worsening of PAH, or initiation need for the prescription of treatment with parenteral prostanoids, or long-term oxygen therapy, or the need for lung transplantation, or balloon atrial septostomy) (HR0.60; 99%CI0.46–0.78; p<0.001). As for background PAH therapy as of the time of enrolment, the reduction in primary endpoints in Selexipag group vs. placebo group was observed irrespective (p for interaction 0.95) of whether the patients had received ERA (HR0.66; 99% CI0.32–1.35), PDE5 inhibitors (HR0.58; 99%CI0.37–0.91), combination of ERA and PDE5 inhibitors (HR0.63; 99%CI0.39–1.01), or no PAH-specific therapy at all (HR0.57; 99%CI0.32–1.03) [5]. The positive effect of the Selexipag usage was observed throughout the maintenance dose range, which supports dosage adjustment [5]. In the GRIPHON study, PAH patients generally demonstrated satisfactory tolerability of oral selexipag, and the most common adverse effects included headache, diarrhea, nausea [5, 7]. In our patient, the addition of

TABLE 6. RISK STRATIFICATION

Determinants of prognosis (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of heart failure	Absent	Absent	Present
Symptoms progression	No	Slow	Rapid
Syncope	No	Occasional syncope	Repeated syncope
Functional class (WHO)	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 ml/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.9	Peak VO_2 <11 ml/min/kg (<35% pred.) VE/VCO_2 ≥45
NT-proBNP plasma levels	BNP <50 pg/l NT-proBNP <300 ng/l	BNP 50–300 ng/l NT-proBNP 300–1,400 ng/l	BNP >300 ng/l NT-proBNP >1,400 ng/l
Imaging (echocardiography, CMR imaging)	RA area<18 cm^2 17.5 No pericardial effusion	RA area 18–26 cm^2 No or minimum pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamic	RAP <8 mm Hg	ДПП 8-14 мм рт. ст. CI 2.0-2.4 л/мин/$м^2$ SvO_2 60-65%	ДПП >14 мм рт. ст. CI <2.01 л/мин/$м^2$ SvO_2 <60%

Selexipag to previously prescribed Bosentan has made it possible to stabilize the condition and achieve all the specified therapy treatment goals. And, importantly, the patient received Selexipag in the dose of 1,200 μg, twice daily, which is not the highest dose, however, this did not reduce the treatment positive effect.

CONCLUSION

The currently registered analogues of Prostacyclin are associated with a number of restrictions. The properties of Selexipag include its availability after oral administration and selectivity against IP receptors, which imparts Selexipag the potential of higher efficacy, safety and tolerability. The pre-clinical and clinical data confirm the efficacy of Selexipag as an innovative drug for PAH treatment.

The drug was authorized in the Russian Federation in June 2019, which undoubtedly enhances the opportunities of PAH treatment.

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