https://doi.org/10.38109/2225-1685-2018-1-72-81

ISSN 2225-1685 (Print)
ISSN 2305-0748 (Online)

Gratsianakaya S.Ye., Arkhipova O.A., Ananicheva N.A., Belkorey O.S., Davydov A.I., Martynyuk T.V., Chazova I.Ye.

CASE REPORT: THE POSSIBILITY OF SPECIFIC THERAPY OPTIMIZATION BY SWITCHING FROM BOSENTAN TO MACITENTAN IN A PATIENT WITH CONGENITAL HEART DISEASE AND EISENMENGER SYNDROME

National Medical Research Centre of cardiology of Ministry of Health, Moscow, Russia

ABSTRACT

A patient with pulmonary arterial hypertension (PAH) associated with congenital heart disease (ventricular septal defect) and Eisenmenger syndrome was started on an endothelin receptor antagonist bosentan. With treatment, the patient's condition had been stable, however, by the second year, worsening shortness of breath, reduced exercise tolerance and an increase of the right heart were noted. Bosentan was switched to macitentan. After a year of this pathogenetic therapy, an improvement in functional status was registered. Moreover, while on macitentan, the patient has successfully undergone a gynecological surgical procedure under general anesthesia.

Key words: *Eisenmenger syndrome, macitentan*

Information about authors:

Arkhipova Olga A.	PhD, Researcher of the department of pulmonary hypertension and heart disease of Scientific research institute of clinical cardiology named after A.L. Myasnikov of the National Medical Research Centre of cardiology of Ministry of Health, 121552, Moscow, 3rd Street Cherepkovskaya, 15a.
Davydov Alexander I.	MD, PhD, DSc, professor of medicine at the chair of obstetrics, gynaecology and perinatology,I.M.Sechenov First Moscow State Medical University, 8/2, ul. Trubetskaya, Moscow, 119991, Russian Federation, phone: 8 (499) 782-3341.
Martynyuk Tamila V.	MD, leading researcher, Head of the department of pulmonary hypertension and heart disease of Scientific research institute of clinical cardiology named after A.L. Myasnikov of the National Medical Research Centre of cardiology of Ministry of Health, 121552, Moscow, 3rd Street Cherepkovskaya, 15a.
Ananicheva Natalia A.	MD, high category cardiologist, head of the cardiological department of the S.S. Yudin City Clinical Hospital, Moscow Department of Health Kolomenskii proezd, 4, Moscow, 115446, Russian Federation, 8 (499) 782-30-51, n.ananicheva@mail.ru
Belkorey Olga S.	MD, 1st category physician, cardiologist at the City Polyclinic No 218 8, pr-d Shokal'skogo, Moscow, 127642, Russian Federation, 8 (499) 790-32-68, gp218@zdrav.mos.ru
Chazova Irina Ye.	Academician of Russian Academy of Science, MD, Director of Scientific research institute of clinical cardiology named after A.L. Myasnikov of the National Medical Research Centre of cardiology of Ministry of Health, 121552, Moscow, 3rd Street Cherepkovskaya, 15a.
Responsible for correspondence: Gratsianakaya Ye.	Postgraduate student of the department of pulmonary hypertension and heart disease of Scientific research institute of clinical cardiology named after A.L. Myasnikov of the National Medical Research Centre of cardiology of Ministry of Health, 121552, Moscow, 3rd Street Cherepkovskaya, 15a, s.gratsianskaya@gmail.com, tel. 8-495-414-68-42

✉ **s.gratsianskaya@gmail.com**

For citation: Gratsianakaya S.Ye., Arkhipova O.A., Ananicheva N.A. et al. Case report: the possibility of specific therapy optimization by switching from bosentan to macitentan in a patient with congenital heart disease and Eisenmenger syndrome. Eurasian heart journal. 2018, February 25; 1:78-81

Pulmonary arterial hypertension (PAH) associated with congenital heart defects (CHD) (PAH-CHD) with the presence of intracardiac or extracardiac shunts is a consequence of constant overload with an elevated volume of the pulmonary circulation and an increase in pulmonary vascular resistance (PVR) [1]. Despite the similarity in terms of histological damage of the lungs, PAH-CHD differs markedly from other forms of PAH. There are four main groups of PAH-CHD in the clinical classification according to the Guidelines of European Society of Cardiology for diagnosis and treatment of PH, 2015: 1) Eisenmenger syndrome; 2) PAH associated with systemic-to-pulmonary shunts; 3) PAH with small, coincidental cardiac defects, 4) PAH after defect closure [2].

Table 1. Indications for use: bosentan vs macitentan

Bosentan	Macitentan
for the treatment of pulmonary arterial hypertension II-IV FC (WHO) in order to improve exercise tolerance and clinical symptoms of adults and children over 2 years	as monotherapy or in combination, is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III to prevent the progression of PAH (death or initiation of intravenous (i.v.) or subcutaneous (s.c.) prostanoids, or atrial septostomy, or lung transplantation, or other worsening of PAH)
- IPAH / heritable; - PAH associated with systemic sclerosis in the absence of significant interstitial lung injury; - PAH, associated with congenital heart disease, in particular, with Eisenmenger syndrome.	- idiopathic and heritable PAH, - PAH, associated with connective tissue diseases, - PAH, associated with a corrected simple congenital heart disease.

A special form of PAH-CHD is Eisenmenger syndrome, which is characterized by an initial systemic-to-pulmonary shunt leading to the progression of PAH, reversion or bi-directional blood bypass and the development of cyanosis. Patients with Eisenmenger syndrome have a vivid symptoms with a low quality of life and severe functional limitations. In addition, the clinical picture besides central cyanosis, dyspnoea, fatigue, may include hemoptysis, syncope, and manifestations of right ventricular heart failure. Reduction in saturation of arterial blood with oxygen leads to disruption of hemostasis, thrombocytopenia, due to which these patients are at risk of developing both bleeding and thrombosis [3]. However, despite pronounced clinical manifestations that reduce the quality of life, the survival of patients with Eisenmenger syndrome is strikingly higher compared with patients with idiopathic PAH (IPAH). Thus, the 5-year survival rate with Eisenmenger syndrome is more than 80%, whereas the 3-year survival with IPAH is 20-30% [4].

After the successful completion of a randomized, double-blind, placebo-controlled study BREATHE-5, bosentan, as a representative of endothelin receptor antagonists (ERA) class, was approved for the therapy of PAH-CHD and Eisenmenger syndrome [5]. Among 54 patients at the 16th week of therapy, bosentan led to a significant decrease in pulmonary vascular resistance and increase a distance in 6-minute work test (6MWT).

In 2015 in our country, a new dual antagonist ET-1 macitentan appeared, which was created to optimize the tissue effects of the drug due to increased lipophilicity [6] (Table 1).

Currently, clinical trials are under way to determine the clinical efficacy of macitentan in case of Eisenmenger syndrome. In addition, clinical data are intensively accumulating in favor of the strategy for switching ERA from bosentan or ambrisentan to macitentan for patients with PAH. Although in the European Guidelines of 2015 this issue is not considered as having no extensive evidence base. Russian experts have developed rules for optimizing therapy, identified categories of patients in need of such tactics (Table 2) [7].

As an example illustrating the possibility and effectiveness of the switching from bosentan to macitentan in the absence of treatment goals, we present the clinical case of a patient with PAH-CHD, Eisenmenger syndrome.

Patient B., born in 1976, is observed in "National Medical Research Center of Cardiology" of the Ministry of Health of the Russian Federation, Institute of Clinical Cardiology named after A.L. Myasnikov since December 2014. It is known that at the age of 1,5 years CHD (ventricular septum defect (VSD)) was revealed. Parents refused from the proposed surgical defect correction at the age of 2 years. Since childhood, the patient has noted exertional dyspnea that caused irregular school attending, lagged behind in physical development from peers. Gradually tolerance to physical activity decreased, cyanosis appeared. High pulmonary hypertension, Eisenmenger syndrome was diagnosed at the age of 10-12

Table 2. Opportunities for optimizing ERA therapy: bosentan/ ambrisentan → macitentan

1. Take into account the profile of drugs interactions (BOSENTAN + SILDENAFIL)

Switching to macitentan is desirable for patients taking bosentan and sildenafil, in connection with the established drug interaction - a change in the pharmacokinetics and, accordingly, the concentration of sildenafil when combined with bosentan.

2. Substitution for macitentan is desirable for patients taking **bosentan and warfarin**, which is often used as symptomatic therapy for patients with PAH and requires careful monitoring of INR.

Taking bosentan, the effectiveness of hormonal contraceptives decreases, which requires the use of dual contraception for women of childbearing age. Macitentan does not affect the pharmacokinetics of warfarin and oral contraceptives.

3. Patients with PAH associated with systemic sclerosis that have the worst prognosis among all etiologies of PAH. Such drugs as macitentan and riociguat, which proved to be effective for long-term outcomes in randomized clinical trials, were suggested to be called drugs of the 2nd generation (unlike 1st-generation drugs - bosentan and sildenafil, affecting mainly the symptoms of PAH).

4. **For newly diagnosed patients with PAH and not previously treated PAH-specific therapy, macitentan should be considered as the first choice drug:** it has the best performance indicators (impact on prognosis - risk and hospitalization rate, risk of morbidity and mortality events), the best profile of drug interactions and tolerability, as well as the proven positive impact on the quality of life of these severe patients.

5. Priority of macitentan on signs of liver function abnormalities of patients with PAH.

Patients who, on the background of bosentan therapy, are noted or previously noted an increase of transaminases, and also in the absence of the possibility of carrying out liver tests.

years. The patient's condition progressively worsened, episodes of hemoptysis periodically began, acrocyanosis increased, and dyspnea increased during physical activities.

On ECHO in 2009, the size of the VSD was 2,5-3,3 cm, a bi-directional discharge, high pulmonary hypertension (sPAP – 80 mmHg) (Eisenmenger syndrome), right heart enlargement, right ventricular hypertrophy, signs of mild level stenosis of the RV output tract.

Due to significant decrease in tolerance to physical activities, chest pain occurrence, episodes of palpitations, edema of the lower limbs, presyncope the patient was first hospitalized to the NMRC of Cardiology in 2014.

According to the physical examination the body mass index was 23 kg /m2, there were acrocyanosis, cyanosis of the distal phalanx of the upper and lower limbs skin, chin, "drumsticks" fingers and "watch glass" nails. In the lungs, breathing was carried out in all departments, with a stiff hue, with breathe rate – 18 per minute. During auscultation, heart sounds were clear, the rhythm was correct; the accent on pulmonary artery. A rough systolic murmur over all auscultation points was heard, with an epicenter along the left edge of the sternum. Blood pressure was 130/80 mm Hg, heart rate – 90 per minute. The abdomen was soft, painless. The liver was not enlarged. There was lower limbs pastosity.

According to electrocardiography (ECG) the rhythm was sinus, heart rate was 77 beat per minute, P-pulmonale atrial component. Right bundle branch block and left antero-upper branch block. Signs of myocardial changes due to right ventricular hypertrophy, signs of combined ventricular hypertrophy (Fig. 1).

According to the results of chest X-ray: lungs are without infiltrative changes. The pulmonary pattern is strengthened due to the vascular component. The signs of PAH are revealed. Pulmonary arteries are not enlarged, the width of the right branch is 16 mm. Cardiothoracic index (CTI) – 51%. Conclusion: right heart enlargement. Arterial pulmonary hypertension (hypovolemia).

On ECHO, CHD has been confirmed: a large VSD (with bi-directional discharge of blood), an overriding aorta, right ventricular hypertrophy, mild pulmonary stenosis, high arterial pulmonary hypertension (Eisenmenger syndrome). The RV hypertrophy (the thickness of the right ventricle anterior wall (TAWRV) was 1.3 cm), the calculated sPAP was 100 mm Hg. On spirometry the pathology was not revealed.

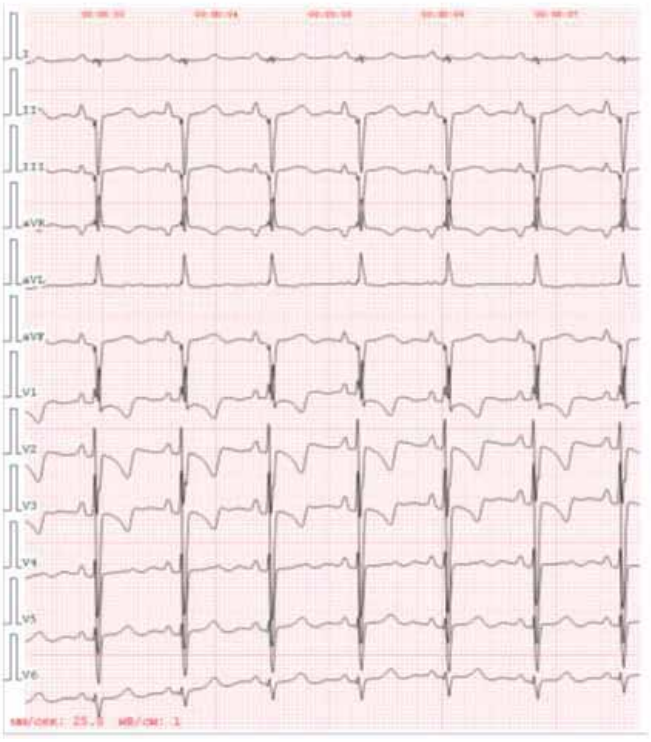

Figure 1. ECG of patient B. (2014).

A ventilation-perfusion lung scan didn't demonstrate acute thromboembolism. There were signs of a blood discharge from the pulmonary to the systemic circulation. A heart magnetic resonance imaging (MRI) demonstrated VSD with bi-directional discharge, the ratio of systemic and pulmonary blood flow is 1: 1,3, a small amount of fluid in the pericardial cavity. Right heart catheterization was not performed due to the lack of evidence. To assess the exercise capacity, a 6-minute walk test was performed to assess the degree of Borg dyspnoea score. The passed distance in the test was 310 meters, dyspnea 3 points (moderate).

Considering the severity of the patient's condition and circulatory insufficiency due to the presence of high pulmonary hypertension and Eisenmenger syndrome, PAH-specific therapy with bosentan at an initial dosage of 125 mg per day was initiated. Considering the signs of circulatory insufficiency, the patient was recommended to take diuretics (spironolactone 25 mg per day, torasemide 2,5 mg 2 times per week).

After discharge, the patient's condition remained stable, but complaints of shortness of breath with minor physical activity, low exercise tolerance remained. In an outpatient setting, the dose of bosentan was not titrated. In December 2015, due to the negative dynamics according to the comprehensive survey (echocardiography, chest X-ray) bosentan was increased to 250 mg per day. However, the walking distance increased to 350 meters (+40 m).

In December 2016, when bosentan therapy was 250 mg per day, negative dynamics were also observed – decreased distance in 6-minute walking test from 350 to 326 m, an increase in sPAP to 115 mm Hg, an enlargement of right heart (according to chest X-ray). Considering the failure to achieve the treatment goals, it was decided to switch from bosentan to macitentan at a dose of 10 mg per day.

In addition, in 2015, the diagnosis of submucosal uterine fibroids has been established. The patient complained of copious uterine bleeding causing iron deficiency. Surgical treatment was recommended, but the latter was not performed because of the high risk of intra- and post-operative complications. The council of physicians decided to perform a surgical intervention in the volume of transcervical myomectomy (hysteroresectoscopy). From the proposed treatment the patient refused. In Russian and International guidelines, the problem of iron deficiency is given special attention. Iron deficiency is defined in 56% of patients with Eisenmenger syndrome. In this category of patients, it has been shown that iron deficiency can lead to a worsening of exercise tolerance and, possibly, an increase in mortality, regardless of the severity of the anemia. It is necessary to monitor regularly the iron level of all patients with PAH for the timely determination of iron deficiency and the appointment of therapy with iron-containing drugs. In a number of studies, it has been shown that absorption of iron is disturbed by PAH, so intravenous administration may be considered preferable, although controlled studies in this area have not been performed [2]. Therefore, the issue of correction of gynecological pathology seemed extremely important.

Later (09.2017) the patient again appealed to the State Clinical hospital named after S.S. Yudin of Moscow Healthcare department, with complaints of increased menstrual bleeding and an even greater reduction in the intermenstrual period. The previous decision of the repeated council of physicians remains in

force, despite a significant increase in the submucosal tumor of the uterus – 58×46 mm. 13.09.17 an operative intervention was made: hysteroresectoscopy. Transcervical myomectomy. Scraping of the mucous membranes of the cervical canal and uterus body. Total ablation of the endometrium. Ligation of descending branches of uterine arteries.

As an anesthetic, general anesthesia with artificial ventilation was chosen. Before induction into general anesthesia, under local anesthesia, a puncture and catheterization of the right radial artery was performed according to the Seldinger method by a 20G catheter, and invasive monitoring of blood pressure was started. Also, before the induction under ultrasound control the right internal jugular vein was punctured and catheterized by a double-lumen catheter, one port of which was used for infusion therapy and drug administration, and the other port for the administration of catecholamines (noradrenaline). Norepinephrine infusion was also started before induction into general anesthesia, in order to maintain a systolic blood pressure above 140 mm Hg and decrease intracardiac discharge from right to left. Surgical intervention was performed in a regular mode with a total duration of 25 minutes, intraoperative blood loss was estimated to be less than 50.0 ml. After the operation, the patient was transferred to the intensive care unit for observation. She was discharged from the hospital on the 3rd day of the postoperative period in a satisfactory condition with recommendations to continue treatment, previously agreed with the cardiologist.

During control examination at the NMRC of Cardiology of the patient receiving macitentan 10 mg per day in 3 months after surgery with general anesthesia ECHO and chest X-ray results remain in a stable state. According to 6-minute walking test the distance increased from 326 m to 350 m. The level of iron is normal.

Thus, this case demonstrates the possibility of switching from bosentan therapy to macitentan in the case of ineffectiveness and failure to achieve goals with bosentan therapy for patients with PAH and Eisenmenger syndrome, this replacement is safe and well tolerated. At the very least, the effectiveness of ERA therapy in terms of impact on exercise tolerance is maintained.

This clinical case corresponds to a prospective observational study of 43 adult patients with PAH (75% with Eisenmenger syndrome, 40% with Down's syndrome), aged 45±13 years who received bosentan therapy on an outpatient basis [8]. The median treatment duration on bosentan was 7.2 years (5.0-8.1). 10 patients (23%) were on bosentan – sildenafil combination therapy. Initially and 6 months after initiation of therapy with macitentan, the following parameters were evaluated: hospitalization for heart failure, syncope, FC III or IV (WHO), 6MWD, oxygen saturation (SaO2), ferritin, NT-proBNP and tricuspid annular plane systolic excursion ring (TAPSE). At 6 months of follow-up, the proportion of patients with FC III-IV (WHO) decreased from 48% to 23% (p = 0.004), NT-pro-BNP levels decreased from 723 ng/l to 488 ng/l (p = 0.019), TAPSE improved from 19±4 to 21±5 mm (p = 0.002). There was good tolerability of therapy with macitentan. Serious adverse events were absent.

Another prospective study included 15 patients with PAH aged 38±16 years who received macitentan therapy [9]. Six patients initially took macitentan, and for nine patients bosentan was switched to macitentan in order to improve drug interactions. The median treatment duration on macitentan was 289 (0-694) days up to end of study. As a result, all patients included in the study had a significant increase 6MWD: from the median at 286 m (120-426) to 360 m (150-450) (p<0.05). SaO2 at rest improved from 83% on average (77-95%) to 91% (77-96%) and after walking from 78% (48-90%) to 79% (62-96%). There were no episodes of liver dysfunction.

In order to evaluate the strategy for optimizing the treatment of ERA for patients with PAH, considering the importance of the problem and the lack of experience with the use of macitentan in clinical practice, it seems efficient to initiate a Russian program for long-term follow-up of such patients under the favour of the National Registry.

BIBLIOGRAPHY

1. *Lowe B.S., Therrien J., Ionescu-Ittu R., et al. Diagnosis of pulmonary hypertension in the congenital heart disease adult population impact on outcomes. J. Am. Coll. Cardiol.2011; 58: 538–546. doi: 10.1016/j.jacc.2011.03.033.*
2. *Chazova I.Ye., Martynyuk T.V., Nakonechnikov S.N. According to the results of the European congress of cardiology 2015: new version of guidelines for diagnosis and treatment of pulmonary hypertension. Eurasian heart journal, 2015; 4: 3-10 [in Russian].*
3. *Chazova I.Ye., Martynyuk T.V. Pulmonary hypertension. M: Practice, 2015 [in Russian].*
4. *Beghetti M., Galiè N. Eisenmenger syndrome a clinical perspective in a new therapeutic era of pulmonary arterial hypertension. J Am Coll Cardiol. 2009 Mar 3; 53(9):733-40. doi: 10.1016/j.jacc.2008.11.025.*
5. *Galiè N., Beghetti M., Gatzoulis M.A. et al. Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study. Circulation. 2006; 114 (1): 48-54.*
6. *Wagner O.F., Christ G., Wojta J. et al. Polar secretion of endothelin-1 by cultured endothelial cells. J Biol Chem 1992; 267:16066–16068.*
7. *T.V. Martynyuk, S.N. Nakonechnikov, I.Ye. Chazova. Optimization of specific therapy for pulmonary arterial hypertension: the possibilities of using endothelin receptor antagonists. Eurasian heart journal, 2017; 2: 20-27 [in Russian].*
8. *Blok I.M., Riel A., A. van Dijk, et al. From bosentan to macitentan for pulmonary arterial hypertension and adult congenital heart disease: Further improvement? Intern J Cardiol 2017; 227: 51-52.*
9. *Herbert, S. et al. Early Experience of Macitentan for Pulmonary Arterial Hypertension in Adult Congenital Heart Disease. Heart, Lung and Circulation, Volume 26, Issue 10, 1113 – 1116.*