https://doi.org/10.38109/2225-1685-2018-2-42-51

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

Check for updates

Devetyarova E.A., Dyuzhikov A.A., Dyuzhikova A.A., Sobin S.V., Sumin A.V., Pashchenko E.V.

CLINICAL CASE OF REPLACEMENT OF ENDOTHELIN RECEPTOR ANTAGONIST (BOSENTAN) BY SOLUBLE GUANYLATE CYCLASE STIMULATOR (RIOCIGUAT) IN THE PATIENT WITH PULMONARY ARTERIAL HYPERTENSION

Rostov region state budgetary institution Rostov region clinical hospital, Rostov-on-Don, Russia

Abstract

Pulmonary arterial hypertension (PAH) is a life-threatening disease characterized by progressive increase in pulmonary vascular resistance (PVR), higher pulmonary arteries mean pressure (mPAP), decrease in cardiac minute output (CMO) and other hemodynamic, functional and biochemical disorders. Existing PAH therapeutic algorithm, described in the European and Russian clinical guidelines, mainly suggest strategy of sequential combination therapy in the case of inadequate response to initial monotherapy. At this, switching from one PAH-specific drug to another is studied to a lesser extent. At the present similar approach (switching) has already been tested, for example, in switching from one endothelin receptor antagonist (ERA) to another, or from phosphodiesterase type 5 inhibitor (iPDE-5) to soluble guanylate cyclase stimulator (sGC). There are virtually no data about change of monotherapy when drugs target different molecular pathways of vascular tone regulation, in particular, in the pulmonary circulation vessels.

This article describes clinical case of female patient with FC III pulmonary arterial hypertension (WHO) switched from therapy by endothelin-1 receptor antagonist (bosentan) to soluble guanylate cyclase stimulator (riociguat). Female, 37 years old, with verified by the right heart catheterization (RHC) diagnosis of idiopathic PAH (iPAH) received PAH-specific monotherapy of bosentan. Due to condition deterioration on the background of bosentan dose increase, medical conference decided to switch this patient to another class of PAH-specific therapy (sGC stimulator riociguat) with consequent follow-up. As a result of such approach positive changes in patient`s condition, improvement of hemodynamic parameters, increased tolerance of physical exercise was demonstrated in comparison with previous therapy.

This clinical case demonstrates safe and successful transfer from bosentan to riociguat in the patient with idiopathic PAH. Similar tactic for the change of therapy should be studied in further clinical trials.

Keywords: *pulmonary hypertension, pulmonary arterial hypertension, riociguat, bosentan, therapy*

Information about authors

Dyuzhikov A.A.	MD, professor, director of the cardiosurgical center of the Rostov Regional Clinical Hospital, tel. 8 (863) 297-02-66, 344015, Rostov-on-Don, Western residential area, Blagodatnaya street, 170
Dyuzhikova A.V.	PhD, doctor of ultrasound diagnostics of the Rostov Regional Clinical Hospital, tel. 8 (863) 224-35-29, 344015, Rostov-on-Don, Western residential area, Blagodatnaya street, 170
Sobin S.V.	PhD, Head of the Cardiology Department №2 of the Rostov Regional Clinical Hospital, tel. 8 (863) 297-02-69, 344015, Rostov-on-Don, Western residential area, Blagodatnaya street, 170
Sumin A.V.	Cardiovascular surgeon, Cardiology Department No. 2 of the Rostov Regional Clinical Hospital, tel. 8 (863) 297-02-69, 344015, Rostov-on-Don, Western residential area, Blagodatnaya street, 170
Pashchenko E.V.	Head of the hospital admission department f the Rostov Regional Clinical Hospital, tel. 8 (863) 224-82-56, 344015, Rostov-on-Don, Western residential area, Blagodatnaya street, 170, e-mail: rokb@aaanet.ru
The author responsible for communication with the editorial staff: Devetyarova E.A.	Cardiologist, Cardiology Department No. 2 of the Rostov Regional Clinical Hospital, tel. 8 (863) 297-02-69, 344015, Rostov-on-Don, Western residential area, Blagodatnaya street, 170; e-mail: helendiamond@yandex.ru

✉ **helendiamond@yandex.ru**

For citation: Devetyarova E.A., Dyuzhikov A.A., Dyuzhikova A.A., Sobin S.V., Sumin A.V., Pashchenko E.V/ Clinical case of replacement of endothelin receptor antagonist (bosentan) by soluble guanylate cyclase stimulator (Riociguat) in the patient with pulmonary arterial hypertension. Eurasian heart journal. 2018, May 25; 2:48-51.

Introduction

Pulmonary hypertension (PH) is a group of diseases characterized by progressive increase in pulmonary vascular resistance (PVR) and pulmonary artery pressure (PAP) leading to development of right-ventricular heart failure and patient`s untimely death [1,2].

Pulmonary arterial hypertension is a clinical condition characterized by presence of precapillary PH in absence of other reasons for higher pulmonary arteries mean pressure (mPAP) such as lung diseases, chronic thromboembolic pulmonary hypertension, etc. including rare diseases [1,2,3].

Depending on its etiology PAH can be idiopathic or hereditary. Also, there are some PAH forms associated with other diseases such as systemic diseases of connective tissue, portal hypertension, HIV infection, congenital heart defects, schistosomiasis. PAH can be also caused by the drugs or toxins exposure, namely by anorectic drugs and other reasons [1,3,11].

PAH pathophysiology is of multi-factor nature and includes higher expression of endothelin-1 vasoconstrictors and thromboxane together with prostacyclin and nitric oxide (NO) deficiency. Along with disbalance of vasoconstrictive and vasodilating factors in PAH, cardiovascular remodeling as adaptive mechanism is also observed. Developed remodeling of pulmonary vessels includes thickening of vessel walls, increase in its resistance and narrowing of arterial lumens which leads to clinically significant disorder of cardiovascular hemodynamics. With progressing of the disease, compensatory tension on the right ventricle (RV) weakens the heart muscle which in the end leads to heart failure [1,12].

PAH is classified among orphan diseases [1]. According to the epidemiological data in general population, PAH prevalence and incidence is 15-60 cases in million and 2.4-10 patients in million annually, accordingly [3].

Hemodynamic PAH is distinguished by presence of mPAP≥25 mmHg, pulmonary artery wedge pressure (PAWP) ≤15 mmHg, PVR >3 Wood units by the data of right heart catheterization in absence of other reasons of PH precapillary form, such as PH due to lung diseases, chronic thromboembolic pulmonary hypertension (CTEPH) other rare diseases [3,4].

Patients usually suffer from dyspnea, lower tolerance of physical exercises, increased fatigue, palpitation, syncopal conditions, chest pain, hemoptysis, lower extremities swelling and other symptoms. Median survival for primary PH without PAH-specific treatment is 2.8 years [1,3,5].

According to the latest European guidelines on diagnosis and treatment of pulmonary hypertension (ESC/ERS 2015), main objective of PAH therapy is a patient achieving low mortality risk for 1 year (<5%) which assumes patient achieving following parameters: I, II WHO FC; distance in 6 minute walk test (6-MWT) >440 m, peak oxygen consumption >15 ml/min/kg; VE/VCO2 slope <36; BNP <50 ng/l; NT-proBNP <300 ng/l; right atrium area <18 cm^2; right atrium pressure <8 mmHg; cardiac index ≥2,5 l/min/m^2; saturation of mixed venous blood >65%; absence of pericardial effusion, absence of symptoms of disease progression, syncopes and clinical signs of the right ventricular heart failure [3,13].

At the present four classes of PAH-specific drugs working due to effect on different targets of vascular tone regulation are widely used in Russia for PH treatment: two stimulators (prostanoids and soluble guanylate cyclase stimulators [sGC] and two inhibitors (endothelin receptor antagonists [ERA] and phosphodiesterase type 5 inhibitor [iPDE-5]). Initial therapy choice is largely defined by WHO FC of the patient. Each of these drug classes has specific molecular target, benefits, and disadvantages. If we take into account special aspects of molecular mode of action, riociguat holds particular interest [1,3,13].

Riociguat is the first representation of the new drug class called soluble guanylate cyclase stimulators. It is known that pulmonary hypertension is associated with endothelial dysfunction and disorders in NO-molecule synthesis which triggers vasodilation process in molecular pathway NO-sGC-cGMP. Riociguat has dual mechanism of action. It sensitizes sGC to the endogenic nitric oxide (NO) by the means of NO-sGC link stabilization; also, riociguat directly stimulates sGC through another binding mechanism, independent of NO. Riociguat restores metabolic pathway NO-sGC-cyclic guanosine monophosphate (cGMP) and causes increase in the cGMP synthesis. Direct stimulation of sGC along with sensibilization of sGC to endogenic NO is a new mechanism of action directed to restore metabolic pathway NO-sGC-cGMP [8,9,14].

In the riociguat clinical trials in patients with PAH, prominent statistically significant improvement of tolerance of physical exercises and improvement of some secondary endpoints including pulmonary hemodynamic, WHO FC and time to clinical deterioration were demonstrated [10].

Clinical case report

Female patient M., 37 years old. According to anamnestic information from 2001, patient for a long time was followed-up and treated by hormonal drugs for tumor of uterus by gynecologist at the place of residence (PoR) after abortion. Before that, the patient didn`t seek medical help. Starting from 2014 patient started to note dyspnea during exercise and visited therapist at the PoR. In 2015 patient was referred to consultation of cardiologist in GBU RO ROKB with dyspnea augmentation. During examination in ROKB distance in 6-MWT 313m; echocardiography (EchoCG) revealed signs of pulmonary hypertension: increase of pressure in RV up to 90 mmHg, TAPSE index 2,4 cm, PA 37mm, systolic mPAP 33mmHg, I-II level PA failure, TV failure level III, RV 50mm, EDV 53ml, EF 50%. Patient was referred to verify PAH diagnosis to the A.N. Bakulev Federal Center of Cardiovascular surgery in Moscow, where she underwent additional examination including right heart catheterization. According to RHC data, systolic PAP 90 mmHg, diastolic PAP 30 mmHg, mPAP 50 mmHg.

Patient was diagnosed with idiopathic pulmonary arterial hypertension. 3 level tricuspid valve failure, 2A circulation failure, FC II. Patient was recommended to start PAH-specific therapy with bosentan 62.5mg twice daily and supporting therapy by amlodipine 2.5mg daily (systemic pressure 136/80 mmHg), warfarin under INR control, diuver. This therapy has been started in October 2015.

In June 2016 during scheduled monitoring, repeated EchoCG was made in GBU RO ROKB. Calculated pressure in the right ventricular on the background of continued therapy increased up to 112 mmHg, and patient was repeatedly referred to the A.N. Bakulev Scientific Center of Cardiovascular surgery to determine further treatment tactic.

In December 2016 patient was examined in out-patient facility of A.N. Bakulev Scientific Center of Cardiovascular surgery: it was noted that distance in 6-MWT decreased down to 308 m; EchoCG – high systolic PAP 114-118 mmHg; SvO2 93-94%. Due to PH progressing it was recommended to increase bosentan dose up to 125mg twice daily.

Starting from January 2017 medical conference at the place of residence decided to increase bosentan dose up to the dose recommended by the Federal Center.

In May 2017 during scheduled periodical examination distance in 6-MWT 310 m; SvO2 94%; EchoCG showed maintained high systolic PAP 112-114 mmHg, mPAP 58 mmHg, TAPSE 2.2 cm, appearance of pericardial effusion up to 10mm of liquid which evidenced further progression of the disease. Therapy was corrected as increase of diuretics dose, replacement of amlodipine by diltiazem while sustaining PAH-specific therapy: bosentan 125 mg twice daily.

After a month in June 2017 the patient was repeatedly examined at the outpatient clinic GBU RO "ROKB". Deterioration of the overall health in the form of augmentation of acute fatigue, dyspnea and decreased tolerance to physical activity were clinically noticed. During the examination: distance in 6 MWT 290 m, SvO2 93%, according to EchoCG systolic PAP 120–125 mm Hg, mean evaluated PAP 58 mm Hg, TAPSE 2.3 cm, liquid remains in the pericardium up to 5 mm. In addition, there was an increase in activity of liver aminotransferases ALT/AST more than 3 times ULN.

Due to absence of the expected effect of bosentan dose increase for 6 months, adverse events, signs of deterioration of the patient's condition, impossibility to add another PAH-specific drug to the received drug for economic reasons a council of physicians made a decision to switch the patient from bosentan to riociguat with dose titration and evaluation of the patient's condition after 3 months. Due to the necessity to receive the drug product at a preferential price and to complete the required documents during a week the dose of bosentan had to be decreased to 62.5 mg 2 times a day to keep the treatment uninterrupted. During the period the patient did not notice significant changes in her condition. After 7 days administration of riociguat was started with initial dose of 1 mg three times a day, which was then titrated according to the scheme described in the drug label.

The dose titration took longer time due to occurrence of hypotension and after 2 weeks of riociguat administration, it was decided to discontinue the calcium channel blocker (diltiazem).

After riociguat therapy initiation the patient noticed gradual improvement of her health condition in the form of some decrease of dyspnea during physical activity, a decrease of acrocyanosis, an increased tolerance to physical activity during a day. Objectively: distance in 6 MWT 350 m, SvO2 96%, according to EchoCG systolic PAP 119-123 mm Hg, TAPSE 2.3 cm, liquid in the pericardium remains.

At the regular patient's visit in December 2017 the following was noticed: distance in 6 MWT 390 m, SvO2 98%, according to EchoCG systolic PAP 118-120 mm Hg, TAPSE 2.3 cm, liquid remains in the pericardium up to 5 mm. The maximum tolerable dose, which was achieved during titration – 2 mg 3 times a day (see Table 1). The patient subjectively informed about improvement of the overall health during riociguat administration, especially in the form of increased tolerability to physical activity. She began to go out of the house, go shopping to buy small things, do simple housework.

On the basis of the received data, the council of physicians decided to continue riociguat therapy and perform dynamic follow-up every 3 months.

After the switch from bosentan to riociguat both improvement of the patient's condition related to treatment with riociguat and favorable safety profile were noticed.

Discussion

Two types of drug therapy are distinguished in patients with PH: a conventional therapy (oral anticoagulants and disaggregants, diuretics, cardiac glycosides, oxygen therapy) and a specific therapy including calcium antagonists, prostanoids, endothelin receptor antagonists (ERA), phosphodiesterase type 5 inhibitors [1].

Recent Russian clinical guidelines for diagnosis and treatment of pulmonary hypertension of 2016 and updated ESC/ERS guigelines on diagnosis and treatment of pulmonary hypertension of 2015 include riociguat as a possible initial monotherapy and as a drug for a sequantial combination therapy with endothelin receptor antagonists (in particular) in PAH patients with FC II-III according to WHO with class of recommendations and level of evidence IB [1,3].

In a randomized, double-blind, international multicenter, placebo-controlled phase III study (PATENT-1) a significant and consistent increase of tolerability to physical activity was noticed during monotherapy with riociguat and, that is important, combination therapy with ERA or prostacyclin analogs. The results showed a 36 m change of 6 MWT distance by week 12 in riociguat group in comparison to placebo ($p<0.001$); a significant decrease of PVR $p<0.001$, least-squares mean difference, -226 dyn×sec×cm-5; 95% CI from -281 to -170; $p<0.001$; a significant decrease of NT-proBNP, least-squares mean difference -432 ng/l, 95% CI from -782 to -82 ($p<0.001$) in riociguat group compared to placebo; significant improvement by at least one FC in riociguat group in 21% of patients, in placebo group – in 14% ($p=0.003$); prolonged time to a clinical deterioration was noticed in riociguat group ($p=0.005$).

Table 1. Parameters of patient condition depending on used therapy and observation period

Observation periods, year		2015[a]	2016[b]	May 2017[c]	June 2017[c]	Sep 2017[d]	Dec 2017[e]
Distance in 6-MWT, m		313	308	310	**290**	350	**390**
Hemodynamic parameters	**SvO_2, %**	-	93-94	94	93	96	**98**
EchoCG	sys.PAP, mmHg	-	114-118	112-114	120-125	119-123	118-120
	mPAP, mmHg	**33**	-	**58**	**58**	-	-
	TAPSE, cm	2.4	-	2.2	2.3	2.3	2.3
	pericardial effusion, mm	no	no	**up to 10**	**up to 5**	**up to 5**	**up to 5**

Note: 6-MWT — test with 6-minute walk; EchoCG — echocardiography; syst.PAP — systolic pressure in pulmonary artery; mPAP — mean pressure in pulmonary artery; TAPSE — tricuspid annular plane systolic excursion, SvO2 — mixed venous blood saturation. [a] without PAH-specific therapy; [b] bosentan 62.5mg BID; [c] bosentan 125mg BID; [d] riociguat; [e] riociguat.

Several other improvements were shown. In longterm study PATENT-2 further improvement of 6 MWT distance and FC were observed. Patient survival was 97% (95% CI 95–98) by the end of the 1 year of the study and 93% (90-95) by the end of the 2 year [10,14,16-18].

At the moment of replacement of bosentan therapy to riociguat described in this clinical case, there were observed no protocols/ algorithms specifying replacement of ERA by soluble guanylate cyclase stimulators. The replacement by riociguat, performed with preliminary decrease of bosentan dose from 125 mg to 62.5 mg two times a day, showed to be safe, successful and to have a potentially positive effect in context of improvement of quality and expectancy of the patient's life.

Conclusions

PAH is a life-threatening condition, which in case of absence of treatment can result in death in the course of 2-3 years – the life expectancy is less than in patients with many different types of malignancies [15,19-20]. This disease requires high awareness and competence of physicians, regular examination and monitoring of patients to detect as early as possible disease progression and adverse events in the setting of administration of prescribed drug products to make therapy adjustments in time. Treatment of this group of patients is complicated by a number of problems related to drug supply.

Due to a severe course of the disease, failure to provide the patient with a combination therapy it was decided to replace bosentan monotherapy by monotherapy with riociguat. This practical solution requires further monitoring of the patient, monitoring of core parameters at a medical setting. Replacement of one class of PAH-specific drugs by another is in some cases an attractive therapeutic option. Nevertheless, this approach should be investigated in course of large-scale randomised controlled studies so that efficacy and safety of such a replacement of drug products may be judged.

REFERENCES

1. *Russian clinical guidelines for the diagnosis and treatment of pulmonary hypertension 2016. Russian Medical Society for Arterial Hypertension. Link: http://cr.rosminzdrav.ru/#!/schema/136 [in Russian].*
2. *Chazova IE, Avdeev SN, Tsareva NA, Volkov AV, Martynyuk TV, Nakonechnikov SN Clinical recommendations for the diagnosis and treatment of pulmonary hypertension. Therapeutic archive. 2014; 9: 4-23 [in Russian].*
3. *Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). EurRespir J. 2015; 46(4):903-75.*
4. *MM Hoeper, HJ Bogaard, R. Condliffe et al. Definitions and Diagnosis of Pulmonary Hypertension. J Am Coll Cardiology. 2013; Vol. 62, Suppl D: D42–50.*
5. *D'Alonzo GE et al. Survival in Patients with Primary Pulmonary Hypertension Ann Intern Med 1991;115:343–349.*
6. *Galie N, Hoeper MM, Humbert M et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J. 2009;30:2493–2537.*
7. *McLaughlin VV, Archer SL, Badesch DB et al. ACCF/AHA 2009expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association: developed in collaboration with the American College of Chest Physicians, American Thoracic Society, Inc., and the Pulmonary Hypertension Association. Circulation. 2009;119:2250–2294*
8. *Humbert M, Ghofrani H-A. The molecular targets of approved treatments for pulmonary arterial hypertension. Thorax. 2016;71:73-83.*
9. *Evgenov OV, Pacher P, Schmidt PM et al. NO-independent stimulators and activators of soluble guanylate cyclase: discovery and therapeutic potential. Nat Rev Drug Discov. 2006;5:755–68.*
10. *Ghofrani HA et al. Riociguat for the Treatment of Pulmonary Arterial Hypertension. N Engl J Med, 2013, 369:330-40. (DOI: 10.1056/NEJMoa1209655) + Protocol + Supplementary appendix.*
11. *Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2013;62(25 suppl D):34D–41D.*
12. *Tuder RM, Archer SL, Dorfmüller P, et al. Relevant issues in the pathology and pathobiology of pulmonary hypertension. J Am Coll Cardiol. 2013;62(25 suppl D):4D–12D.*
13. *Chazova I.Ye., Martynyuk T.V. Pulmonary hypertension. M.: Practice, 2015 [in Russian].*
14. *Адемпас. Инструкция по медицинскому применению лекарственного препарата. ЛП-002639-051017. Источник: http://grls.rosminzdrav.ru/Grls_View_v2.aspx?routingGuid=8bea0e5b-b5d6-4154-b047-f667ce7430d7&t/Adempas. Instructions for the medical use of the medicinal product. LP-002639-051017. Source: http://grls.rosminzdrav.ru/Grls_View_v2.aspx?routingGuid=8bea0e5b-b5d6-4154-b047-f667ce7430d7&t [in Russian].*
15. *Verdecchia A, Francisci S, Brenner H et al. Recent cancer survival in Europe: a 2000–02 period analysis of EUROCARE-4 data. Lancet Oncol/ 2007;8:784–796.*
16. *Ghofrani HA, Galie N, Grimminger F et al. Riociguat for the treatment of pulmonary arterial hypertension: a randomized, double-blind, placebo-controlled study (PATENT-1). Chest. 2013, Atlanta GA, USA, 26–31 October 2013.*
17. *Rubin L, Galie N, Grimminger F et al. Riociguat for the treatment of pulmonary arterial hypertension (PAH): a phase III longterm extension study (PATENT-2). Am J Resp Crit Care Med. 2013;187:A3531.*
18. *Hossein-Ardeschir Ghofrani et al. Predictors of long-term outcomes in patients treated with riociguat for pulmonary arterial hypertension: data from the PATENT-2 open-label, randomised, long-term extension trial. Lancet Respir Med. 2016; 4:361–371.*
19. *D'Alonzo GE, Barst RJ, Ayres SM et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. Ann Intern Med. 1991;115:343-349.*
20. *Thenappan T, Shah SJ, Rich S et al. Survival in pulmonary arterial hypertension: a reappraisal of the NIH risk stratification equation. Eur Respir J. 2010;35:1079–1087.*

Accepted for publication: April 27, 2018