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Dynamics of the clinical functional and hemodynamic profile of patients with pulmonary arterial hypertension with initial monotherapy with endothelin receptor antagonists: bosentan vs. macitentan

Aim	To compare results of 24-h treatments with bosentan and macitentan by the clinical functional status and indexes of pulmonary hemodynamics in patients with pulmonary arterial hypertension (PAH).
Materials and methods	Based on the Russian National Registry (NCT03707561), 44 patients older than 18 years with PAH (34 patients with idiopathic pulmonary hypertension (IPH) and 10 patients with Eisenmenger syndrome) were retrospectively included into this study. Based on the statistical method of pairwise comparison, two groups were formed and matched by age, gender, WHO functional class (FC), and 6-min walk distance (6MWD). 22 patients of group 1 (17 with IPH and 5 with Eisenmenger syndrome) were treated with macitentan 10 mg/day, and 22 patients of group 2 (17 with IPH and 5 with Eisenmenger syndrome) were treated with bosentan 250 mg/day. Clinical instrumental data (6MWD, Borg dyspnea score, chest X-ray, transthoracic echocardiography (EchoCG), and right heart catheterization (RHC)) were evaluated at baseline and after 24 weeks of therapy.
Results	By week 24 of the treatment, FC and 6MWD improved in both groups. The macitentan treatment was associated with a significant decrease in Borg score. Significant intergroup differences in EchoCG data were not observed. The bosentan treatment was associated with a decrease in right ventricular (RV) dimension and a tendency towards a decrease in calculated pulmonary artery systolic pressure (PASP). By week 24, the macitentan treatment as compared to the bosentan treatment, was associated with a decrease in cardiothoracic ratio (CTR). In both groups, RHC showed decreases in PASP, mean pulmonary artery pressure and pulmonary vascular resistance, and improvements in cardiac output (CO), cardiac index, and stroke volume (SV) values. By week 24, the increase in SV was greater in the macitentan treatment group than in the bosentan treatment group (p=0.05).
Conclusion	The 24-week treatment with bosentan or macitentan provided significant and comparable improvement of the functional profile in PAH patients with FC II (WHO) at baseline. The decrease in CTR was significantly more pronounced in the macitental treatment group compared to the bosentan treatment group. The 24-week bosentan treatment resulted in a decrease in RV anterior-posterior dimension, a tendency towards a decrease in PASP according to EchoCG data. Macitentan provided more pronounced dynamics of dyspnea than bosentan according to the results of 6MWD test and the increase in SV according to RHC data.

Keywords	Pulmonary arterial hypertension; idiopathic pulmonary hypertension; Eisenmenger syndrome; endothelin receptor antagonists; bosentan; macitentan
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Introduction

Pulmonary arterial hypertension (PAH) is a severe progressive disease which leads to right-sided heart failure [1, 2]. The possibilities of drug therapy for this category of patients for a long time were significantly limited prior to the introduction of PAH-specific drugs into clinical practice. Modern specific therapy has an impact on the pathogenesis of PAH, including the activation of the endothelin-1 system involved in the remodeling of small pulmonary arteries and arterioles leading to vasoconstriction of the distal pulmonary arterial bed [1–3].

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Activation of the endothelin system in patients with PAH serves as a rationale for the active clinical use of the endothelin receptor antagonists (ERAs) [1, 4–6]. Bosentan is the first non-selective ERA approved by the Pharmacological Committee of the Russian Federation to treat patients with idiopathic pulmonary arterial hypertension (IPAH), scleroderma-related PAH without severe pulmonary fibrosis and Eisenmenger syndrome aimed at improving exercise tolerance and slow disease progression.

Macitentan is a new potent ERA designed to increase the efficacy and safety of therapy due to its high tissue specificity. The increased proportion of non-ionized forms of the molecule improves the physical and chemical properties of the drug thus contributing to higher penetration of the drug through lipophilic cell membranes and increases the tissue penetration of the drug [7–9]. The landmark randomized trial SERAPHIN was conducted to assess the effect of macitentan on morbidity and mortality and included 742 patients with PAH. The use of macitentan at a daily dose of 10 mg compared to a placebo resulted in a 45% reduction in the risk of disease progression [4, 10].

Both bosentan and macitentan are currently commonly used in clinical practice for the treatment of patients with PAH. However, there is an apparent lack of direct comparative studies.

The objective of our study was to conduct a comparative analysis of the clinical, functional, and hemodynamic profiles of patients with PAH treated with various ERAs (bosentan or macitentan) for 24 weeks.

Materials and Methods

The local ethics committee of Myasnikov Institute of Clinical Cardiology approved the study. It was concluded that the study was conducted pursuant to the principles of the Declaration of Helsinki. In this study, two groups were formed retrospectively based on the pairwise comparison within the Russian national register (NCT03707561). The groups were comparable in age, sex, World Health Organization (WHO) functional class (FC), and 6-minute walk test (6MWT). In Group 1, 22 patients (17 – IPAH, 5 – Eisenmenger syndrome) received macitentan 10 mg/day. In Group 2, 22 patients (17 – IPAH, 5 – Eisenmenger syndrome) received bosentan 250 mg/day. The duration of treatment was 24 weeks in both groups. A total of 44 patients were included, if they met the following inclusion criteria: age >18 years; verified diagnosis of IPAH or Eisenmenger syndrome; FC (WHO) II–III; negative vasoreactivity test with inhaled nitric oxide or iloprost during right heart catheterization (RHC); standard drug therapy (diuretics, glycosides, anticoagulants, or antiplatelet agents) within the past 3 months; stable course of the disease during specific therapy. The exclusion criteria were age <18 years; PAH of other etiology; pulmonary hypertension (PH) due to left heart disease or lung diseases and/or hypoxia; chronic thromboembolic PH; non-compliance with contraception by female patients of childbearing age; pregnancy, lactation; hypertension; persistent hypotension, systolic blood pressure <90 mm Hg; musculoskeletal diseases interfering with the 6-minute walk test; increased levels of aspartate aminotransferase and/or alanine aminotransferase of more than 3 times; anemia (hemoglobin <100 g/L).

The clinical, laboratory, instrumental, and hemodynamic parameters and survival rates were assessed in this study. Patients underwent such studies as 6MWT with the Borg dyspnea score, chest x-ray, echocardigraphy, RHC.

The statistical analysis of findings was carried out using Statistica 10.0 (StatSoft, USA). The level of statistical significance was $p<0.05$. The Student's t-test was used to compare the normally distributed quantitative variables between the patient groups. Non-parametric statistical tests (Mann–Whitney and Wilcoxon) were used for non-normal distributions. The quantitative variables are expressed as the median and the interquartile range (25^{th} and 75^{th} percentiles). The categorical variables are presented by the distribution frequencies. Pearson's χ^2 test was used to compare the categorical variables.

Results

The groups of patients were comparable by sex (91% of female patients), mean age (39.7±11.9 and 40.0±12.6 years old in Groups 1 and 2, respectively), FC (WHO), and 6MWT (402.4±53.6 and 405.2±56.4 m in Groups 1 and 2, respectively) at the time of inclusion.

The period from the onset of the disease to the verification of the diagnosis of PH (13 [7; 37] and 14.5 [5; 48] months ($p=0.93$) in Groups 1 and 2, respectively), and the time from the first symptoms to the start of macitentan/bosentan therapy (58 [5; 48] and 84 [17; 213] months ($p=0.68$) in Groups 1 and 2, respectively) did not differ between the groups.

The most common complaint was shortness of breath (100% in Group 1 and 95% in Group 2). Patients also complained of chest pain, palpitations, dizziness, and asthenia. Upon inclusion in the study, 27% of patients in the bosentan group and 45% in the macitentan group had edema of the lower extremities (Figure 1).

Figure 1. Patient's complaints upon inclusion

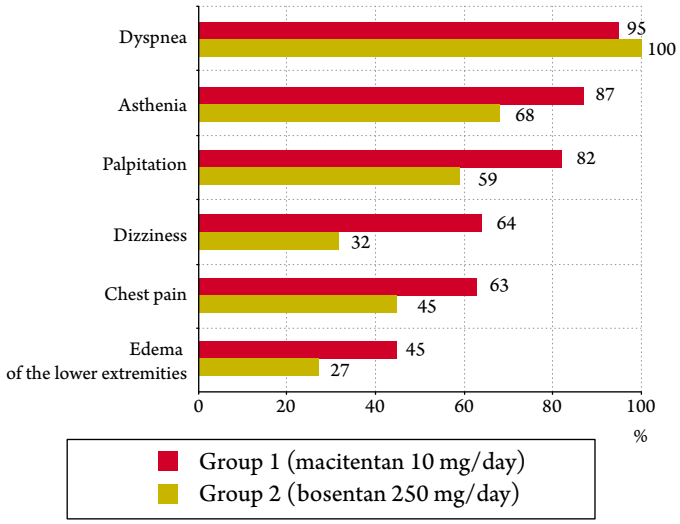
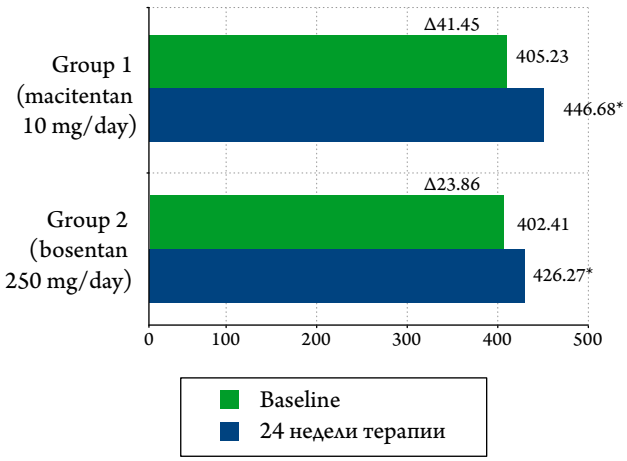


Figure 2. Changes in the 6MWT performance in patients treated with bosentan/macitentan at baseline and week 24



*, p < 0.05 — the significance of intragroup differences at baseline and week 24.

When the patient's functional class was assessed on Week 24, 6MWT increased by 41.45 m (p=0.00009) and 23.86 m (p=0.034) in the macitentan and bosentan groups, respectively (Figure 2). The groups did not differ in changes in the 6MWT performance (p=0.42). On Week 24, the Borg dyspnea score was significantly lower in the macitentan group (2.95±1.40 and 3.95±1.96 (p=0.048) in Groups 1 and 2, respectively).

An improvement in FC (WHO) was noted in the macitentan group by Week 24 of the follow-up: 23% of patients reached FC I (WHO), the number of patients with FC III (WHO) decreased by 67% (FC I/II/III/IV (WHO) 0/10/12/0 at baseline, 5/13/4/0 on Week 24) fewer patients reached FC I (WHO) in the bosentan group (FC I/II/III/IV (WHO) 0/11/11/0 at baseline, 3/13/6/0 on Week 24).

No significant differences were found in the chest x-ray findings between the groups on Week 24 of follow-up (Table 1). On Week 24, a decrease in the cardiothoracic ratio (CTR) was more significant in the macitentan group than in the bosentan group (p=0.04).

Baseline echocardiography detected signs of an increase in the right heart dimensions, right ventricular (RV) hypertrophy, and increased pulmonary artery systolic pressure (PASP) in both groups. The RV dimensions decreased (p=0.03) by Week 24th in the bosentan group, although there were differences in the changes of the RV dimensions between the bosentan and macitentan groups (p=0.56). Other echocardiographic parameters did not differ significantly either at baseline or after 24 weeks of treatment (Table 2).

Such pulmonary hemodynamic parameters as PASP, mean pulmonary artery pressure (mPAP), cardiac output (CO), cardiac index (CI), and pulmonary vascular resistance (PVR) improved by Week 24, as shown by RHC (Table 3).

Changes in the hemodynamic profiles (RHC) were compared, and it was noted that 24-week treatment with macitentan resulted in a more significant increase in stroke volume (SV) versus the bosentan treatment (p=0.05) (Figures 3, 4).

Table 1. Changes in the chest x-ray findings in patients treated with bosentan/macitentan at baseline and week 24

Parameter	Group 1 (macitentan 10 mg/day)		p	Group 2 (bosentan 250 mg/day)		p
	Baseline	24 weeks		Baseline	24 weeks	
Right descending PA diameter, mm	19.15±6.67	19.23±6.35	0.84	19.45±5.16	19.57±4.72	0.79
Moore, %	39.18±8.80	38.36±9.60	0.25	35.86±6.31	37.31±8.01	0.07
Lupi,%	36.22±4.42	36.05±3.95	0.62	36.45±3.17	35.41±4.47	0.23
CTI,%	52.14±6.77	51.73±6.36	0.44	49.36±4.32	49.22±4.66	0.83

PA, pulmonary artery; CTR, cardiothoracic ratio.

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Литература: 1. Galiè N., Humbert M., Vachiery J.L. et al. Eur Heart J 2016; 37: 67-119. 2. Simonneau G. et al. Eur Respir J 2015; 46 (6): 1711-20. 3. Jansa P., Pulido T. Am J Cardiovasc Drugs 2018; 18: 1-11.
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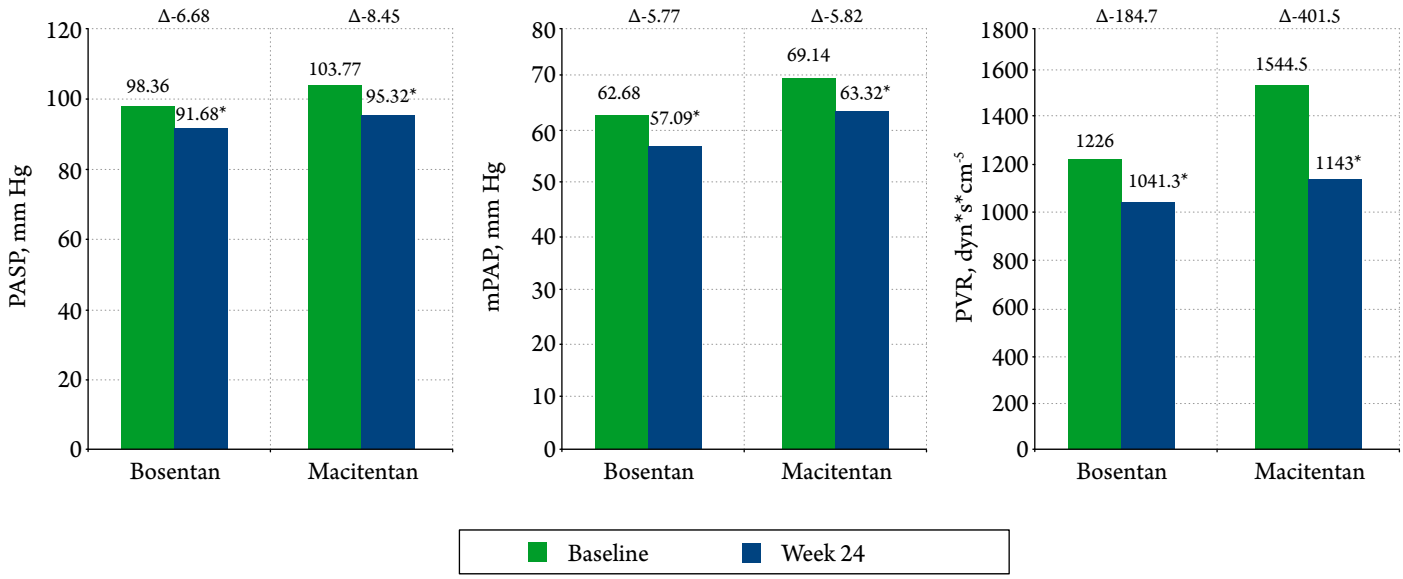
Figure 3. Changes in PASP, mPAP, PVR according to RHC in patients treated with bosentan/macitentan at baseline and week 24



*, p < 0.05 — the significance of intragroup differences at baseline and week 24.

Table 2. Changes in the transthoracic echocardiogram in patients treated with bosentan/macitentan at baseline and week 24

Parameter	Group 1 (macitentan 10 mg/day)		p	Group 2 (bosentan 250 mg/day)		p
	Baseline	24 weeks		Baseline	24 weeks	
LA, cm	3.32±0.65	3.34±0.56	0.61	3.28±0.56	3.27±0.60	0.87
LVEDD, cm	3.81±0.55	3.91±0.61	0.09	3.92±0.53	4.00±0.48	0.52
RA area, cm2	21.10±7.03	21.48±7.25	0.42	21.05±7.74	20.80±9.00	0.58
RV APD, cm	3.50±0.60	3.50±0.80	0.96	3.88±0.78	3.63±0.80	0.03*
RV AWT, cm	0.82±0.23	0.81±0.24	0.70	0.75±0.23	0.76±0.19	0.68
PA diameter, cm	3.30±0.78	3.25±0.85	0.40	3.39±0.73	3.45±0.68	0.39
SPAP, mm Hg	98.40±26.13	93.64±27.12	0.29	92.22±22.34	86.59±19.28	0.06
IVC, cm	2.05±0.40	2.05±0.40	1.00	2.10±0.42	2.00±0.39	0.09

*, p <0.05, the significance of intragroup differences at baseline and on week 24. LA, left atrium, RV, right atrium, LV EDD, left ventricular end-diastolic dimension, RV APD, right ventricular anterior-posterior dimension, RV AWT, right ventricular anterior wall thickness, PA, pulmonary artery, IVC, inferior vena cava, PASP, pulmonary artery systolic pressure.

Table 3. Changes in the right heart catheterization in patients treated with bosentan/macitentan at baseline and week 24

Parameter	Group 1 (macitentan 10 mg/day)		p	Group 2 (bosentan 250 mg/day)		p
	Baseline	24 weeks		Baseline	24 weeks	
PASP, mm Hg	103.77±27.90	95.32±27.80	0.0225*	98.36±25.93	91.68±22.25	0.0074*
mPAP, mm Hg	69.14±20.33	63.32±18.27	0.0083*	62.86±17.62	57.09±15.93	0.0001*
PAOP, mmHg	6.27±2.16	6.22±3.24	0.9539	7.09±4.30	7.89±4.01	0.4979
SaO_2, %	95.18±3.59	94.00±4.72	0.0542	93.73±5.49	92.06±7.99	0.2938
SvO_2, %	63.36±5.82	67.14±5.86	0.0008*	62.77±6.99	66.05±7.50	0.0032*
CO, L/min	3.43±0.95	4.40±0.99	0.0002*	3.65±0.87	4.12±1.02	0.0031*
CI	1.97±0.43	2.57±0.57	0.00003*	2.16±0.43	2.55±0.90	0.0076*
SV, L/min/m^2	43.21±11.59	58.11±16.34	0.0002*	48.65±16.27	55.82±18.48	0.0004*
PVR, dyn*s*cm^{-5}	1544.5±583.96	1143.0±646.42	0.00001*	1226±511.64	1041.30±489.64	0.0107*

*, p <0.05 – the significance of intragroup differences at baseline and on week 24; mPAP – mean pulmonary artery pressure; PAOP, pulmonary artery occlusion pressure; SaO2, arterial oxygen saturation; SvO_2, venous oxygen saturation; CO, cardiac output; CI, cardiac index; SV, stroke volume; PVR, pulmonary vascular resistance.

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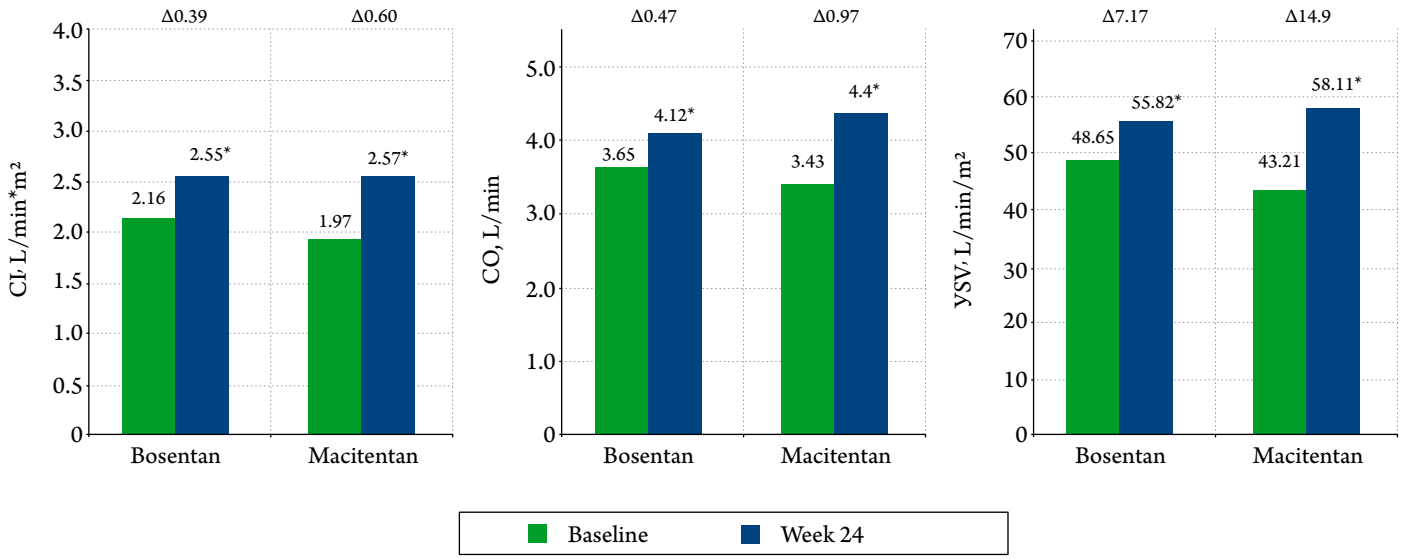
Figure 4. Changes in CI, CO, SV according to RHC in patients treated with bosentan/macitentan at baseline and week 24



*, p < 0.05 — the significance of intragroup differences at baseline and week 24.

On Week 24, three patients in the bosentan group and two patients in the macitentan group required an escalation of the PAH-specific therapy.

Treatment with both bosentan and macitentan was not accompanied by adverse reactions. Monthly monitoring of hepatic transaminases showed no clinically significant changes. The 24-week survival rate was 100% in both groups.

Discussion

The efficacy and safety of both bosentan and macitentan therapy in patients with PAH have been studied in several pilot studies and large randomized clinical trials [1, 4, 11–14]. However, there is currently an apparent lack of studies directly comparing the efficacy of bosentan and macitentan in patients with PAH, leading to a need to conduct such studies. In this study, the efficacy of 24-week initial therapy with macitentan and bosentan in patients with PAH (IPAH, Eisenmenger syndrome) was compared.

The 24-week treatment with bosentan and macitentan improved functional status and findings from clinical examination.

The 6MWT performance significantly increased by 23.86 m, and FC (WHO) improved in the bosentan group. There was a significant decrease in the RV anterior-posterior size (–0.25 cm) and a tendency towards a decrease in the estimated PASP (–5.63 mm Hg, p=0.06) according to echocardiography data. RHC showed an improvement in the pulmonary hemodynamic profile resulting in a decrease in PASP (–6.68 mmHg), mPAP (–5.77 mmHg), PVR (–184.7 dyn×s×cm^{-5}), an increase in CI (+0.39 L/min×m^2), CO (+0.47 L/min), SV (+7.17 L/min/m^2), and venous blood saturation (+3.28%).

A pilot study previously performed at Myasnikov Institute of Clinical Cardiology to assess the efficacy of 12-week bosentan therapy in patients with PAH and baseline FC II (35.3%), III (47.1%), and IV (17.6%) also showed a statistically significant decrease in FC (WHO) both in the group of patients receiving bosentan 125 mg/day and those receiving bosentan 250 mg/day. Moreover, a statistically significant decrease in PASP (–5.4 mmHg) was observed in patients who received bosentan 125 mg/day [11, 12]. There were no statistically significant differences among patients taking the recommended dose of 250 mg/day. The mean decrease in mPAP in the BREATHE-1 study (–6.7 mm Hg) is comparable to the previous findings [11, 12]. The delta of PVR reduction in this study was slightly lower, and the absolute value of the PVR achieved was slightly higher (936.9±400.2 dyn×sec/cm^{-5}) than in the first study performed at the Myasnikov Institute of Clinical Cardiology [2, 12].

The 24-week bosentan therapy improved FC (WHO) similar to the other studies: 16% of patients achieved FC I, and the number of patients with FC III fell 2.1 times. In our study, the 6MWT distance increased by 23.86 m, slightly less than in the BREATHE-1 study (44 m) and the Russian pilot study (46.4 m) [11, 12].

The 24-week treatment with both bosentan and macitentan resulted in a reduction of the cardiometric values. The changes in CTR were more significant in the macitentan group. In previous studies, the changes

in cardiometric parameters based on the results of chest x-ray were not analyzed.

In the macitentan group (10 mg/day for 24 weeks), FC (WHO) and the 6MWT performance (+41.45 m) improved, as well as hemodynamic profiles according to RHC: a decrease in PASP (–8.45 mm Hg), mPAP (–5.82 mm Hg), PVR (–401.5 dyn×s×cm^{-5}), an increase in CI (+0.6 L/min×m^2), CO (+0.97 l/min), SV (+14.9 L/min/m^2), and venous blood saturation (+3.78%).

Hemodynamic subanalysis in the first randomized clinical trial SERAPHIN (Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome) showed a significant decrease in mPAP (–6.4 mm Hg) and an increase in CI (+0.63 L/min/m^2), consistent with our findings [13]. However, there was a more significant decrease in PVR (401.5 dyn×s×cm^{-5}) in our study. It would be interesting to compare our results to the findings of Tahara et al. That study included patients with PAH mainly of FC II (53.3%) and III (43.3%), who received initial therapy with macitentan 10 mg/day for 24 weeks, increasing CI by 0.41 L/min×m^2 and reducing mPAP by 6.0 mm Hg and PVR by 250 dyn×s×cm^{-5}. The 24-week therapy increased the 6MWT performance by 67 m and the FC improvement in 46.4% of patients [14].

There was a more significant decrease in the Borg dyspnea score and significantly higher values of SV among patients who received macitentan 10 mg/day for 24 weeks, shown by comparing the bosentan and macitentan groups. Other comparable measures were similar across the groups.

The 24-week survival rate was 100% in both groups. Moreover, no adverse events were reported in both the bozentan group and the macitentan group.

Limitations

The study was limited by the absence of randomization, small sample, and the retrospective analysis.

Conclusion

Thus, the 24-week therapy with ERAs, such as bosentan and macitentan, can improve the functional status of patients with IPAH and FC II–III (WHO) PAH with Eisenmenger syndrome. Macitentan reduces the severity of dyspnea significantly more than bosentan in this group of patients. After 24 weeks of therapy, 23% of patients achieved FC I (WHO), and the proportion of patients with FC III (WHO) decreased by 67% in the macitentan group.

Macitentan improves cardiometric parameters, unlike bosentan; notably by Week 24 the CTR values decreased in the macitentan group.

Patients who were treated with bosentan for 24 weeks showed recovery of RV remodeling and a tendency towards a decrease in the estimated PASP according to echocardiographic data.

Pulmonary hemodynamics significantly improved by Week 24 of bosentan and macitentan therapy. Moreover, there is a more significant increase in SV during the use of macitentan versus bosentan.

Both bosentan and macitentan showed good tolerability. The 24-week survival rate in both groups was 100%.

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REFERENCES

1. Galiè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A 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): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). European Heart Journal. 2016;37(1):67–119. DOI: 10.1093/eurheartj/ehv317
2. Martynyuk T.V. Pulmonary hypertension: diagnosis and treatment. – M.: LLC Medical news Agency;2018. - 304 p. [Russian: Мартынюк Т.В. Легочная гипертензия: диагностика и лечение. – М.: ООО «Медицинское информационное агентство», 2018. – 304 с]. ISBN 978-5-604-00080-9
3. Chazova I.E., Avdeev S.N., Tsareva N.A., Volkov A.V., Martynyuk T.V., Nakonechnikov S.N. Clinical practice guidelines for the diagnosis and treatment of pulmonary hypertension. Therapeutic archive. 2014;86(9):4–23. [Russian: Чазова И.Е., Авдеев С.Н., Царева Н.А., Волков А.В., Мартынюк Т.В., Наконечников С.Н. Клинические рекомендации по диагностике и лечению легочной гипертонии. Терапевтический архив. 2014;86(9):4-23]
4. Pulido T, Adzerikho I, Channick RN, Delcroix M, Galiè N, Ghofrani H-A et al. Macitentan and Morbidity and Mortality in Pulmonary Arterial Hypertension. New England Journal of Medicine. 2013;369(9):809–18. DOI: 10.1056/NEJMoa1213917
5. Clozel M, Breu V, Burri K, Cassal J-M, Fischli W, Gray GA et al. Pathophysiological role of endothelin revealed by the first orally active endothelin receptor antagonist. Nature. 1993;365(6448):759–61. DOI: 10.1038/365759a0
6. Stewart DJ. Endothelin in cardiopulmonary disease: factor paracrine vs neurohumoral. European Heart Journal. 1993;14(Suppl I):48–54. PMID: 7904941
7. Iglarz M, Binkert C, Morrison K, Fischli W, Gatfield J, Treiber A et al. Pharmacology of Macitentan, an Orally Active Tissue-Targeting Dual Endothelin Receptor Antagonist. Journal of Pharmacology and Experimental Therapeutics. 2008;327(3):736–45. DOI: 10.1124/jpet.108.142976
8. Raja SG. Macitentan, a tissue-targeting endothelin receptor antagonist for the potential oral treatment of pulmonary arterial hypertension and idiopathic pulmonary fibrosis. Current Opinion in Investigational Drugs. 2010;11(9):1066–73. PMID: 20730702

ISSN 0022-9040. Kardiologiia. 2020;60(7). DOI: 10.18087/cardio.2020.7.n1136

9. Wagner OF, Christ G, Wojta J, Vierhapper H, Parzer S, Nowotny PJ et al. Polar secretion of endothelin-1 by cultured endothelial cells. The Journal of Biological Chemistry. 1992;267(23):16066–8. PMID: 1644793
10. Martynyuk T.V., Nakonechnikov S.N., Chazova I.E. Optimization of specific therapy for pulmonary arterial hypertension: the possibilities of using endothelin receptor antagonists. Eurasian Cardiology Journal. 2017;2:20–7. [Russian: Мартынюк Т.В., Наконечников С.Н., Чазова И.Е. Оптимизация специфической терапии легочной артериальной гипертензии: возможности применения антагонистов рецепторов эндотелина. Евразийский кардиологический журнал. 2017;2:20-7]
11. Channick RN, Simonneau G, Sitbon O, Robbins IM, Frost A, Tapson VF et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebocontrolled study. The Lancet. 2001;358(9288):1119–23. DOI: 10.1016/S0140-6736(01)06250-X
12. Martynyuk T.V., Arkhipova O.A., Kobal E.A., Eruslanova K.A., Danilov N.M., Chazova I.E. Use of non-selective endothelin receptor antagonist bosentan in patients with idiopathic pulmonary hypertension: the first Russian experience and look into the future. Systemic Hypertension. 2011;8(4):51–7. [Russian: Мартынюк Т.В., Архипова О.А., Кобаль Е.А., Ерусланова К.А., Данилов Н.М., Чазова И.Е. Применение неселективного антагониста рецепторов эндотелина бозентана у больных идиопатической легочной гипертензией: первый Российский опыт и взгляд в будущее. Системные гипертензии. 2011;8(4):51–7]
13. Galiè N, Jansa P, Pulido T, Channick RN, Delcroix M, Ghofrani H-A et al. SERAPHIN haemodynamic substudy: the effect of the dual endothelin receptor antagonist macitentan on haemodynamic parameters and NT-proBNP levels and their association with disease progression in patients with pulmonary arterial hypertension. European Heart Journal. 2017;38(15):1147–55. DOI: 10.1093/eurheartj/ehx025
14. Tahara N, Dobashi H, Fukuda K, Funauchi M, Hatano M, Ikeda S et al. Efficacy and Safety of a Novel Endothelin Receptor Antagonist, Macitentan, in Japanese Patients with Pulmonary Arterial Hypertension. Circulation Journal. 2016;80(6):1478–83. DOI: 10.1253/circj.CJ-15-1305