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Research Article

The Effectiveness of the Drug Uperio and Angiotensin-Converting Enzyme Inhibitors during Dilated Cardiomyopathy Complicated by Chronic Heart Failure

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ABSTRACT

Introduction. One of the urgent problems in modern cardiology is the diagnosis of chronic heart failure (CHF) in the early stages of development and, therefore, improving the prognosis and quality of life of patients. The most significant reasons for the development of heart failure at a relatively young age include dilated cardiomyopathy (DCM), which manifests itself only with the development of heart failure. Clinical recommendations of recent decades dictate the need for the appointment of angiotensin-converting enzyme (ACE) inhibitors for the treatment of heart failure. In 2014, the results of a large randomized, double-blind clinical trial of PARADIGM-HF were published, during which the efficacy of standard therapy of heart failure with ACE inhibitors was compared with the new generation drug therapy Uperio.

The purpose of this study is to compare the effect of the drug Uperio and ACE inhibitors on the course of DCM complicated by heart failure, according to the level of NT-proBNP and the value of hemodynamic parameters.

Materials and methods. 32 patients with DCM complicated by heart failure were monitored in 2 groups: the main group (patients treated with Uperio) and the control group (patients treated with ACE inhibitors). Before the start of treatment and after its completion, an assessment of the clinical condition, an electrocardiographic and echocardiographic study, determination of the level of NT-proBNP in all patients were carried out.

Research results and conclusions. Therapy with a new generation of Uperio leads to a more significant improvement in the clinical condition of patients with DCM than ACE inhibitors, reducing the intensity of shortness of breath by 78.1 and 65.6%, respectively. A more effective decrease in the level of NT-proBNP (by 47 and 22%, respectively) and an increase in the ejection fraction (by 10.2 and 6.3%, respectively) by the time of discharge in the group of patients taking Uperio were observed compared with the group of patients taking inhibitors ACE.

Keywords: cardiomyopathy, heart failure, ejection fraction, efficacy, NT-proBNP, therapy.

INTRODUCTION

Dilated cardiomyopathy (DCM) is a complex, etiologically heterogeneous myocardial disease characterized by dilatation of the left ventricle (LV) or biventricular dilatation with severe systolic dysfunction in the absence of hemodynamic overload factors (hypertension, valvular defects, congenital malformations of the heart) or coronary pathology (coronary heart disease).

DCM is one of the most formidable, progressive and prognostically unfavorable diseases of the heart muscle, leading to the development of chronic heart failure (CHF), rhythm and conduction disturbances, and, ultimately, to heart transplantation. DCM is the most common form of cardiomyopathy (over 60%), which occurs with a frequency of 3-5 to 11-13 cases per 100,000 population [2].

Despite great progress in the diagnosis of cardiovascular diseases, there are no clear criteria to establish a diagnosis of DCM in the early stages. In most cases, DCM manifests with signs of heart failure, the treatment of which is mainly aimed at therapy. However, the prognosis for these patients is very unfavorable: mortality

over a 5-year period with any functional class (FC) of heart failure is 50% among men and 46% among women [3].

The clinical picture of heart failure is very subjective, and routine methods (radiography, electrocardiography, echocardiography) have a number of significant drawbacks. At present, assessment of natriuretic peptides (NT-proBNP), a marker of heart failure and directly related to the prognosis and survival of patients, has been put into practice: the higher it is, the more severe heart failure [4]. J. Cleland (2004) notes the importance of determining the level of natriuretic peptides in patients with heart failure along with determining the number of leukocytes in patients with pneumonia [5].

Angiotensin-converting enzyme (ACE) inhibitors, which significantly reduce the mortality of patients by 16% in patients with mild to moderate insufficiency, have been the basis in the treatment of heart failure for several decades. With the development of adverse events when taking drugs of this group (mainly dry cough), it is recommended that they be replaced with angiotensin receptor blockers [6].

Over the past few years, Uperio has been introduced into clinical practice, consisting of an inhibitor of neprilysin sacubitrile and an antagonist of receptors for angiotensin II (ARA) valsartan. The effectiveness and safety of this drug are addressed in several multicenter studies.

In a prospective, double-blind clinical trial PARADIGM-HF (2014), conducted to compare the effects of Uperio (LCZ696) and an ACE inhibitor enalapril on the prognosis of patients with heart failure, 8399 patients with heart failure of the II, III and IV class on the Killip scale took part with a reduced ejection fraction (EF) (less than 40%). The study confidently showed that, compared with enalapril, the drug Uperio reduced the risk of cardiovascular mortality by 20% (13.3% versus 16.5%; p <0.0001), and the risk of rehospitalization by 21% (12.8 % versus 15.6%; p <0.0001).

A multicenter, randomized, open-label study TRANSITION (2018), involving 1002 patients with heart failure with a reduced ejection fraction of the left ventricle, hospitalized due to acute decompensated heart failure, showed that therapy with Uperio is safe and appropriate to start both in a hospital after stabilization of the patient, and soon after discharge on an outpatient basis. Moreover, the study notes that the proportion of patients who stopped taking the drug due to adverse events was less than 5% [7].

In another multicenter, randomized, double-blind study of PIONEER-HF (2018), involving 881 patients with CHF, the efficacy of the valsartan + sacubitrile complex was compared with enalapril for NT-proBNP changes. Already in the first week of the study, the difference in the decrease in the level of natriuretic peptide between the groups was 24% [8].

At the congress of The European Society of Cardiology 2019, the results of the III phase of a randomized, double-blind, actively controlled study of PARAGON-HF were presented with the participation of 4822 patients with heart failure with preserved ejection fraction. The study evaluated the efficacy and safety of the combined drug Uperio compared with valsartan. It was noted that the valsartan + sacubitrile complex is more effective in lowering the level of NT-proBNP than valsartan by the 12th week, and improving the functional class of heart failure by the 36th week. The most significant effects of Uperio were recorded in patients with a left ventricular ejection fraction of 57% or less (p = 0.0140) [9].

The purpose of the study is to compare the effectiveness of Uperio and ACE inhibitors in the course of DCM complicated by heart failure, in terms of NT-proBNP and hemodynamic parameters.

MATERIALS AND METHODS

32 patients with DCM complicated by heart failure with a reduced left ventricular ejection fraction (21 men and 11 women) aged 34 to 78 years with a disease duration of 2-4 years were monitored.

All patients were divided into 2 groups: 16 patients treated with Uperio at a dosage of 200 mg twice a day (main group) and 16 patients in the control group treated with ACE inhibitors (enalapril 10 mg twice a day, lisinopril 20 mg two once a day). The dose was selected by titration. The duration of therapy was 4 weeks.

The criteria for inclusion and exclusion of patients from the study are presented in table 1.

Table 1: Study inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Confirmed diagnosis of DCM with a disease duration of 2 years or more; The presence of complications in the form of heart failure according to NYHA FC II-IV;	Hypersensitivity to the components of the drug Uperio (valsartan and / or sakubitril); Symptomatic hypotension and / or systolic blood pressure level of less than 100 mm Hg;

Age over 18 years; Left ventricular ejection fraction - 40% or less over the past 6 months; Level NT-proBNP 1600 pg / ml or more; Hospitalization for acute decompensated heart failure; Stabilization of the condition in a hospital 24 hours before randomization and corresponding to one of the criteria: therapy with ACE inhibitors or ARA before admission to the hospital (at any dosage); lack of therapy with ACE or ARA inhibitors; the absence of ACE or ARA inhibitors at least 4 weeks before hospitalization.	The terminal stage of chronic renal failure (glomerular filtration rate less than 30 ml / min / 1.73 m^2); The level of potassium (K^+) in the blood serum is more than 5.4 mmol / l; The presence in the history of a case of angioedema (during therapy with ACE inhibitors or ARA); Severe liver pathology: the level of total bilirubin is 50 μmol / l or more, signs of liver cirrhosis (expansion of the lower veins of the esophagus); Acute coronary syndrome, acute cerebrovascular accident, transient ischemic attack; Isolated right ventricular heart failure (associated with bronchopulmonary pathology).

All patients were also divided into groups according to the classification of the New York Heart Association (NYHA): CHF II FC - 6 (18.7%), CHF III FC - 15 (43.8%), CHF IV FC - 11 (37.5%). Patients were hospitalized in two clinical bases - in the Republican Clinical Hospital State Health Institution of the Ministry of Health of the Republic of North Ossetia-Alania and in the clinical hospital of the North Ossetian State Medical Academy. In all patients, before and after treatment, the clinical condition was assessed during the collection of complaints and anamnesis, an electrocardiographic study (ECG), assessment of central hemodynamics by echocardiography indicators: left ventricular ejection fraction (LVEF), left ventricular shortening fraction (LVSF), end systolic diameter ESD and diastolic diameter (EDD), end systolic (ESV) and end diastolic (EDV) volumes, the thickness of the interventricular septum (IVS) and the posterior wall of left ventricle (PWLV). The mass of the left ventricular myocardium (LVM) was calculated by the formula: $LVM = 0,8 \cdot (1,04 \cdot (IVS + EDD + PWLV)^3 - EDD^3)) + 0,6$. The severity of heart failure was also determined by the level of NT-proBNP.

Statistical processing of the data obtained during the clinical study was carried out using the applied statistical programs Microsoft Excel and Statistica for Windows 10.0. $p = 0.05$ is taken as the threshold value of the critical significance level (p) when testing statistical hypotheses.

RESEARCH RESULTS AND DISCUSSION

Among the examined, the proportion of men was 66%, women - 34%. More than half (62.5%) of patients were people in the age category of 50-60 years.

During a general clinical study of patients, their main complaints were identified: shortness of breath during little physical exertion (93.7%), sharp general weakness (96.8%), palpitations (65.6%), "interruptions" in the heart (56, 2%), swelling in the legs (68.7%), periodic pain in the heart region of a different nature and intensity (59.4%).

On the ECG, the majority of the examined had various rhythm and conduction disturbances: extrasystole - in 62.5%, atrial fibrillation - in 28.1%. 84.4% of patients showed signs of left ventricular hypertrophy.

According to the results of echocardiography (table 2), there was an increase in the size of the left ventricle: EDD (73.1 mm), ESD (59.2 mm), as well as a decrease in the contractility of the left ventricular myocardium: EF (30.3%) and SF (14 ,5%). No increase in PWLV and IVS was detected (10.3 and 10.2, respectively). At the same time, an increase was also observed in LVM (153.8).

Table 2: Indicators of central hemodynamics in patients with DCM before treatment

Indicators	Results	p
EDD, mm	73,4±0,5	< 0,001
ESD, mm	55,9±0,4	< 0,001
EDV, ml	232,3±4,13	< 0,001
ESV, ml	142,1±2,61	< 0,001

EF, %	35,8±1,15	< 0,001
SF, %	17,8±0,74	< 0,001
PWLV, mm	10,3±0,1	< 0,001
IVS, mm	10,2±0,2	< 0,001
LVM	153,8±3,73	< 0,001

Moreover, the corresponding data of central hemodynamics were obtained in patients with various FC CHF (according to NYHA) (table 3).

Table 3: Indices of central hemodynamics in patients with DCM with various FC CHF

Indicators	CHF II FC	CHF III FC	CHF IV FC
EDD, mm	68,1	72,4	79,8
ESD, mm	52,2	54,1	61,3
EDV, ml	210,4	239,9	246,8
ESV, ml	131,3	141,0	154,2
EF, %	40,1	36,8	30,4
SF, %	21,5	17,4	14,5

Comparing the CHF III FC, LV dilatation is more pronounced (EDD 72.4; ESD 54.1; EDV 239.9; ESV 141.0), a decrease in cardiac inotropic function (EF 36.8 ; SF 17.4).

A comparative analysis of indicators of patients with CHF III and IV FC revealed a significant increase in size (EDD 79.8; ESD 61.3) and volumes (EDV 246.8; ESV 154.2) LV, as well as a decrease in EF (30.4) and SF (14.5) in patients with FC IV CHF.

Thus, as CHF progresses in patients with DCM, a pronounced dilatation of the heart cavities develops, accompanied by a decrease in systolic function. In most patients with FC II CHF, remodeling is adaptive in nature, aimed at maintaining an adequate cardiac output. With the development of CHF IV FC, the compensatory capabilities of the body are exhausted, and the process of remodeling becomes maladaptive.

The severity of heart failure was also established by the level of NT-proBNP, the average level of which in patients upon admission was 2150 pg / ml (table 4).

Table 4: The average level of NT-proBNP in patients with DCM complicated by heart failure

Indicator	CHF II FC	CHF III FC	CHF IV FC
NT-proBNP, pg/ml	1650	2032	2770

Chest x-ray revealed the expansion of the borders of the heart in 31 patients (96.8%).

A significant change in clinical, hemodynamic and laboratory parameters was noted as a result of treatment of patients (table 5).

Table 5: Clinical, hemodynamic and laboratory parameters in patients with DCM complicated by heart failure after treatment with ACE inhibitors and Uperio

Indicators	Before treatment	ACE inhibitors	Uperio
Shortness of breath during mild exertion,%	93,7	28,1	15,6
Sharp general weakness,%	96,8	31,2	21,9
EDD, mm	73,4±0,5	67,3±0,5	60,5±0,5
ESD, mm	55,9±0,4	50,3±0,4	47,4±0,4

EDV, ml	232,3±4,13	214,7±4,13	197±4,13
ESV, ml	142,1±2,61	124,2±2,61	109,6±2,61
EF, %	35,8±1,15	42,1±1,15	46,0±1,15
SF, %	17,8±0,74	22,9±0,74	27,4±0,74
NT-proBNP, pg/ml	2150	1677	1139,5

During therapy with ACE inhibitors, dyspnea intensity decreased in 21 (65.6%) patients, and EF increased on average by 6.3% and amounted to 42.1 ± 1.15 ($p < 0.001$). The decrease in the level of NT-proBNP at the time of discharge was 22% (1677 pg / ml).

Moreover, in patients taking the drug Uperio, dyspnea intensity decreased in 25 (78.1%) patients. EF in patients increased by an average of 10.2% and amounted to 46.0 ± 1.15 ($p < 0.001$). The level of NT-proBNP already by the time of discharge from the hospital decreased significantly - by 47% (1139.5 pg / ml).

Thus, the difference in the decrease in the level of NT-proBNP between the main and control groups was 25%.

CONCLUSION

As a result of the study, it was found that therapy with the new generation of Uperio leads to a more significant improvement in the clinical condition of patients with DCM, reducing the severity of symptoms of heart failure than therapy with ACE inhibitors. A more effective decrease in the level of NT-proBNP and an increase in EF by the time of discharge in the group of patients taking Uperio were noted compared with the group of patients taking ACE inhibitors. Thus, patients receiving therapy with Uperio are prescribed with a much more favorable prognosis of CHF in the presence of DCM.

Conflict of interest: The authors declare no conflicts of interest.

REFERENCES

1. Vaykhanskaya T.G., Sivitskaya L.N., Kurushko T.V., Levdansky O.D. Dilated cardiomyopathy: a new look at the problem. Russian Journal of Cardiology. No. 24 (4). 2019. Pp. 35-47.
2. Kruchinkina E.V., Ryabova T.R., Batalov R.E. Modern approaches in the treatment of patients with decompensated heart failure. Bulletin of Siberian medicine. No. 17 (4). 2018. Pp. 238-253.
3. Filippov E.V., Yakushin S.S. Dilated cardiomyopathy: differential diagnosis, approaches to therapy, surgical treatment. Cardiology: news, opinions, training. No. 2. 2017. Pp. 91-103.
4. Melnik A.A. Natriuretic peptides in the diagnosis of heart failure. Medicinal newspaper "Healthy Ukraine". No. 22 (347). 2014. Pp. 24-25.
5. Cleland J.C.F., Goode K. Natriuretic peptides for heart failure. Fashionable? Useful? Necessary? European Journal of Heart Failure. Vol. 6. 2004. Pp. 253-256.
6. John J.V. McMurray, Milton Packer, Akshay S. Desai, Jiannjian Gong, Martin P. Lefkowitz, Adel R. Rizkala. Inhibitor of neprilysin and angiotensin receptors compared with enalapril in heart failure. The New England Journal of Medicine. No. 11. 2014. Pp. 993-1004.
7. Velarques E.I., Morrow D.A., DeVore A.D., Duffy C.I. Angiotensin-Neprilysin Inhibition in Acute Decompensated Heart Failure. The New England Journal of Medicine. No. 6. 2019. Pp. 539-548.
8. Wachter R. TRANSITION primary data poster presentation (P886). ESC Congress, Munich, Germany. 2018.
9. Solomon S., McMurray J., Anand I., Jundo Ge Angiotensin-Neprilysin in Heart Failure with Preserved Ejection Fraction. The New England Journal of Medicine. No.17. 2019. Pp. 1609-1620.
10. Panagov Z.G., Sanova A.Z., Uzalaeva Sh.A. Clinical and hemodynamic features of the course of dilated cardiomyopathy. 58 final student scientific conference with international participation "Time to look to the future ...". Vladikavkaz: SOGMA. 2019. Pp. 58-59.
11. Astakhova Z.T., Zagalova D.S. The use of an inhibitor of the angiotensin-converting enzyme zofenopril in the treatment of chronic heart failure on the background of DCM. Russian Journal of Cardiology. No. 2 (82). 2010. Pp. 74-77.
12. Piano M.R. Alcoholic Cardiomyopathy: Is it Time for Genetic Testing? Journal of the American College of Cardiology. No. 20. 2018. Pp. 2303-2305.
13. Santosh kumar maurya, anil kumar singh, ankit seth (2015) potential medicinal plants for lymphatic filariasis: a review. Journal of Critical Reviews, 2 (1), 1-6.