

Evaluation of Pulmonary Vasodilator Therapy with Endothelin-Receptor Antagonist in Eisenmenger Syndrome

Togănel Rodica¹, Făgărășan Amalia¹, Muntean Iolanda¹, Șuteu Carmen², Blesneac Cristina³, Sglimbea Anca¹, Gozar Liliana², Pașc Sorina², Koncsag-Szasz E.³

¹ University of Medicine and Pharmacy Tg. Mures, Department of Paediatric Illrd

² Pediatric Cardiology Department, Institute of Cardiovascular Disease and Transplant Tg. Mureș

³ County Emergency Clinic Hospital Tg. Mureș

Objective: To assess the effect of treatment with endothelin-receptor antagonists on patients with Eisenmenger syndrome, by monitoring oxygen saturation, exercise capacity and echocardiography.

Methods: A total of 14 pediatric patients diagnosed with Eisenmenger syndrome were evaluated clinically by systemic pulse-oximetry, 6-minute walk test and by echocardiography at the beginning of pulmonary vasodilator treatment with endothelin-receptor antagonist, at 3 and 6 months after treatment initiation.

Results: NYHA functional class, systemic arterial blood saturation and distance walked in 6 minutes improved after 3 and 6 months of pulmonary vasodilator treatment. In our study we observed that Tei index right ventricle has improved after 3 months of therapy. We found no statistically significant changes in other ecocardiographic parameters of pulmonary hypertension evaluation.

Conclusions: Endothelin-receptor antagonist improved exercise capacity and hemodynamics, without compromising peripheral oxygen saturation.

Keywords: Eisenmenger syndrome, endothelin receptor antagonist

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Introduction

Pulmonary arterial hypertension (PAH) is a rare condition characterized by extensive remodelling of the pulmonary vasculature, and, if not treated, it results in right heart failure and death. PAH is defined as a mean pulmonary artery pressure of > 25 mmHg at rest, or > 30 mmHg with exercise in the absence of increased left-sided pressure. Congenital heart disease, left-to-right shunts in particular, can be complicated by the emergence of PAH, which under certain conditions may progress to Eisenmenger physiology with reversal of the shunts. This condition is defined as a congenital heart defect that 1/ initially caused a major left-to-right shunt, 2/ induces severe pulmonary vascular disease and PAH, and 3/ finally results in reversal of the direction of shunting and development of cyanosis [1, 2].

Eisenmenger syndrome is a multisystem disorder associated with numerous life-threatening complications: hemoptysis, cerebrovascular accidents, brain abscesses, arrhythmias, and syncope [1]. In most patients with Eisenmenger syndrome exercise capacity is severely impaired.

Endothelin-1 is produced primarily by vascular endothelial cells and acts as powerful vasoconstrictor and mitogen for smooth muscle [2]. The endothelin-1 system appears to be intimately involved in the pathophysiology of PAH, and in patients with Eisenmenger syndrome an elevated endothelin-1 plasma and tissue levels have been observed. Accordingly, patients with PAH associated to congenital heart disease may benefit from endothelin receptor antagonists.

The endothelin receptor antagonists have been shown to improve haemodynamics, functional status, six-minute walk test, quality of life, right ventricular reverse remodeling and survival in patients with either idiopathic PAH, or the variant due to connective tissue disease [3, 4, 5, 6, 7, 8]. Patients with Eisenmenger syndrome have largely been excluded from trials of PAH. It is not certain whether endothelin receptor antagonists may also improve outcomes for patients with Eisenmenger syndrome. Four preliminary reports suggest that treatment with endothelin receptor antagonists administered over 3 to 10 months was safe, well-tolerated, and possibly beneficial in patients with Eisenmenger syndrome [3, 9, 10, 11, 12].

Echocardiography represents one of the non-invasive procedures which offers useful information regarding the correct quantification of the stages of PAH, the adaptative pathophysiological modifications and the identification of structural and functional cardiac modifications associated with pulmonary vasodilator therapy. Although several authors have drawn attention to the key role of echocardiography in the management of PAH, its present role is still a restricted one [13, 14, 15]. Although numerous treatments have been introduced with subtle improvements in echocardiographic parameters, the prognosis of the disease remains somber [13, 16, 17]. In the literature, five echocardiographic parameters have been described as associated with mortality in PAH: degree of pericardial effusion [18, 19, 20], right atrial area indexed to body surface area [20], end-diastolic eccentricity index [20], right ventricular Tei

index [21], and tricuspid annular plane systolic excursion (TAPSE) [22]. The clinician needs objective parameters in order to detect worsening of the patient's condition as early as possible and initiate optimal treatment.

The aim of our observational, uncontrolled study was to document the effect of treatment with endothelin receptor antagonists on functional class, transcutaneous saturation of oxygen and six-minute walk distance in patients with Eisenmenger syndrome and to identify which echocardiographic parameter has improved significantly.

Materials and methods

Selection of patients

A total of 14 patients with median age of 11.2 years diagnosed with Eisenmenger syndrome were assessed clinically, by systemic pulse oximetry, 6-minute walk test and by echocardiography at the beginning of pulmonary vasodilator treatment with endothelin-receptor antagonist, at 3 and 6 months after treatment initiation. PAH was confirmed by cardiac catheterization, as mean pulmonary arterial pressure (MPAP) > 25 mmHg, pulmonary capillary wedge pressure < 15 mmHg, and pulmonary vascular resistance (PVR) > 3 UWood.

Eisenmenger syndrome was due to ventricular septal defect in 7 patients, double inlet left ventricle with transposition of the great arteries in 2 patients, atrioventricular septal defect in 1 case, truncus arteriosus type IV in 1 case, persistent ductus arteriosus in 1 patient, single ventricle with single atrioventricular connection - 1 case, corrected transposition of great artery with large ventricular septal defect in 1 case.

All patients had dyspnoea on exercise. 8 patients were in NYHA III functional class, and 6 patients were in NYHA IV functional class at the beginning of treatment with endothelin-receptor antagonist.

The baseline saturation of oxygen in room air, at rest was between 70–98%, with a median value of 83%, and the baseline 6 minute walk distance was between 216 m and 450 m.

All patients were assessed by echocardiography using a 33 IE Phillips Device, at the time of initiation of endothelin-receptor antagonist therapy, at 3 months and 6 months of treatment. Data were collected according to a pre-established protocol: measurement of systolic pulmonary arterial pressure (PASP) from tricuspid regurgitation flow, of diastolic pulmonary arterial pressure (PADP) and MPAP from pulmonary regurgitation flow. We estimated the right atrial pressure by measuring the inferior vena cava (IVC) diameter in under-costal view and studying respiratory variations in IVC diameter. We evaluated the echocardiographic parameters of the right ventricle (RV) function: TAPSE with M mod cursor placed through the lateral tricuspid annulus in apical-4 chamber view and Tei index = RV myocardial performance index, reflecting global RV performance. For the assessment of RV function we also analyzed the end-diastolic and end-systolic interventricu-

lar septal curve in parasternal short axis view. Pulmonary artery acceleration time (PAAcT) was determined by tire anterograd Doppler flow in the pulmonary artery.

The PVR was echocardiographically estimated, by dividing PASP with velocity time integral (VTI) in right ventricular outflow tract (RVOT).

The legal guardians of the enlisted patients signed a form of consent in conformity with the norms of the Ethical Committee of the University of Medicine and Pharmacy from Tirgu Mures. The recommendation for initiating the endothelin-receptor antagonist therapy was correlated with recommendations of specialist guides and protocols.

Statistical analysis

The descriptive and comparative statistical analysis was performed with SPSS software. The distribution was not normal in some subgroups so we used a non-parametric model (Friedman test) for testing the difference among values measured at 0, 3 and 6 months.

Results

Functional class

At baseline, 8 patients (55%) were in NYHA III functional class, and the other 6 patients were in NYHA IV functional class. At 3 months of treatment with endothelin-receptor antagonist, 6 patients (45%) had improved NYHA functional class, in 2 cases from NYHA III to NYHA II, and in 4 cases from NYHA IV to NYHA III. The functional class remained the same at 6 months of treatment (Table I).

Systemic pulse oximetry

After 3 months of treatment we observed a minimal increase in systemic oxygen saturation, from median baseline values of 81% to 81.73%. After 6 months of treatment evaluation of systemic arterial blood saturation shows a statistically significant improvement, with a median value of 84% ($p = 0.006$) (Figure no 1). In a single case, oxygen saturation had a decrease from baseline value after 6 months of pulmonary vasodilator therapy. These results confirm that treatment with endothelin-receptor antagonists does not reduce systemic arterial blood oxygen saturation [1] (Figure 1).

Exercise capacity

After 3 months of treatment with endothelin-receptor antagonists the mean distance walked in 6 minutes was increased by 39m, from a median value of 346 m to 385 m, whereas after 6 months of treatment a statistically significant improvement in the walked distance was observed, respectively an increase of 59 m, to a median value of 405 m ($p = 0.004$) (Figure 2).

Echocardiography

Our echocardiographic evaluation reveals that Tei index, reflecting global RV performance has shown a change after

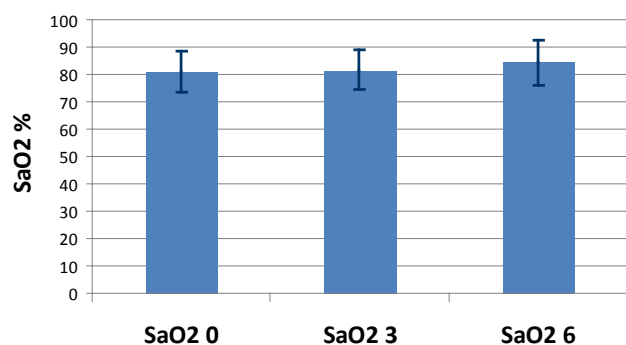


Fig. 1. Evolution of SaO₂ from baseline to 3 and 6 months of treatment

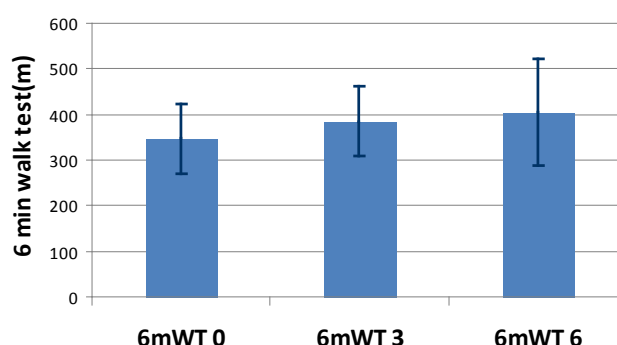


Fig. 2. Evolution of 6 minute walk test from baseline to 3 and 6 months of treatment

3 months of treatment with endothelin-receptor antagonist, therefore median of the index has improved from a baseline value of 0.61 to 0.53. This value remained unchanged after 6 months of treatment (Figure 3).

No statistically significant changes were found in other echocardiographic parameters quantified at baseline, 3 months and 6 months of pulmonary vasodilator therapy.

Endothelin-receptor antagonists were well tolerated in all cases, with no side effects registered.

Discussion

Three classes of drugs targeting the modification of endothelial dysfunction have been recently approved in the treatment of PAH: prostanoids, endothelin receptor antagonists and phosphodiesterase type 5 inhibitors. Their efficacy and safety have been demonstrated in PAH associated with congenital heart disease and in Eisenmenger syndrome, mostly by uncontrolled studies.

Only one randomized, controlled trial including 54 patients has reported a favorable effect on exercise capacity and hemodynamics of the treatment with the orally active dual endothelin-receptor antagonist in Eisenmenger patients, confirming uncontrolled studies [1]. Compared with placebo, endothelin receptor antagonist significantly reduced pulmonary vascular resistance and mean pulmonary arterial pressure and significantly increased 6-minute

walk distance, without compromising peripheral oxygen saturation [1].

In our study we showed that the beneficial effect of treatment with endothelin-receptor antagonist is the improvement of 6 minute walk distance.

Endothelin-receptor antagonist therapy was shown to improve exercise capacity and cardio-pulmonary hemodynamics in the preliminary study of patients with PAH [23]. In the first multicentric, randomized, double-blind, placebo-controlled trial for adults with Eisenmenger syndrome, endothelin-receptor antagonist therapy significantly improved hemodynamics and exercise capacity without adversely affecting systemic arterial oxygen saturations [1]. Gatzoulis et al. treated 10 patients with endothelin-receptor antagonists, reporting an improvement of mean 6-minute walk distance, of resting oxygen saturation and echocardiographic parameters after 3 months of treatment [11]. Two other preliminary reports suggest similar findings [10, 11, 12].

Randomized clinical trials assessing pulmonary vasodilator therapy in children with PAH are in progress.

We found that treatment with endothelin-receptor antagonists was associated with mild, but significant improvement in oxygenation at rest. This increase in oxygenation was accompanied by an improvement in functional status. Although this was an uncontrolled observational study, the

Table I: Evolution of NYHA functional class from baseline to 3 months of treatment

	Diagnosis	Age (years)	Sex	NYHA baseline	NYHA at 3 months
1.	VSD	16	F	IV	III
2.	VSD	6	M	III	III
3.	DILV. TGA	15	F	IV	IV
4.	TGA anatomically corrected. VSD. ASD. PDA	9	F	IV	III
5.	DILV. TGA. DOWN sdr	9	M	III	III
6.	AVSD	9	M	III	III
7.	VSD	6	F	IV	III
8.	VSD. ASD	15	M	IV	IV
9.	TAC TYPE IV.	9	F	III	III
10.	SV. MITRAL ATHRESIA. VSD. ASD	17	F	IV	III
11.	VSD	17	F	III	II
12.	PDA	17	F	III	III
13.	VSD. ASD	6	M	III	II
14.	VSD. DOWN sdr	7	M	III	III

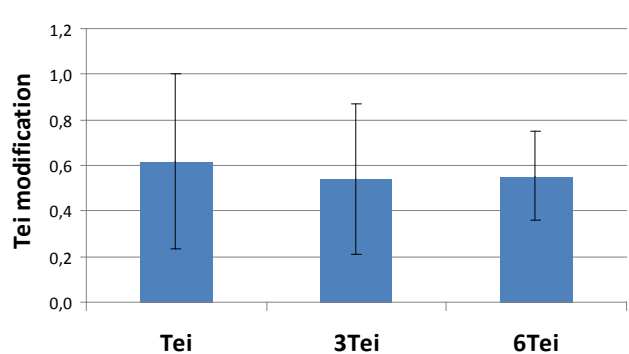


Fig. 3. Evolution of Tei index from baseline to 3 and 6 months of treatment

improvement was similar to that reported in recent trials of endothelin-receptor antagonist in patients with idiopathic PAH [4, 5, 24].

The six minute walk test is a reliable tool for the assessment of exercise capacity in patients with PAH, furthermore it is an independent predictor of mortality [25, 26, 27].

The Tei index, reflecting global RV performance, had already been described as a predictor of mortality in a study by Yeo et al [21]. In our findings we observed that Tei index had improved after 3 months of endothelin-receptor antagonist therapy.

The limits of our study relate primarily to the relatively small number of patients enrolled (14 children), to the fact that the study was conducted in a single center. Further, extended studies are necessary.

Conclusion

In this study, the orally administrated endothelin-receptor antagonist to patients with Eisenmenger syndrome produced favorable hemodynamic and functional effects that were similar to those reported in other randomized studies of other forms of PAH. Endothelin-receptor antagonists decreased the proportion of patients in NYHA IV functional class, suggesting that it may slow the progression of the disease. Nevertheless, long term clinical experience is still needed.

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