Initial experiences with the treatment of pulmonary arterial hypertension in congenital heart disease in Slovenia

Prve izkušnje z zdravljenjem pljučne arterijske hipertenzije pri bolnikih s prirojenimi srčnimi napakami v Sloveniji

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Izvleček

Izhodišča: Pljučna arterijska hipertenzija, katere najbolj napredovala oblika je Eisenmengerjev sindrom, je pomemben zaplet pri bolnikih s prirojenimi srčnimi napakami. Poleg podpornega zdravljenja so v zadnjih letih na voljo tudi specifična zdravila za zdravljenje pljučne arterijske hipertenzije. Analizirali smo učinkovitost in varnost zdravljenja s specifičnimi zdravili pri naših bolnikih s pljučno arterijsko hipertenzijo, povezano s prirojenimi srčnimi napakami.

Metode: V analizo smo vključili bolnike, ki so od novembra 2007 do decembra 2011 prejemali specifična zdravila za zdravljenje pljučne arterijske hipertenzije. Spremljali smo klinično stanje, zasičenost kisika, merjeno s pulznim oksimetrom, prehojeno razdaljo pri šestminutnem testu hoje in nekatere laboratorijske kazalnike. Analizirali smo rezultate zdravljenja po 3, 6, 12 in 24 mesecih in jih primerjali glede na izhodiščne vrednosti.

Rezultati: V opazovanem obdobju smo 23 bolnikov zdravili s specifičnimi zdravili za pljučno arterijsko hipertenzijo. Devetnajstim bolnikom smo uvedli bosentan, štirim pa sildenafil. Zaradi kliničnega poslabšanja smo 4 bolnikom dodali drugo zdravilo, eni bolnici pa dodatno še dve zdravili. Osemnajstim bolnikom (78,3 %) se je ob zdravljenju izboljšala telesna zmogljivost. Dva bolnika (8,6 %) sta umrla. Prehojena razdalja pri šestminutnem testu hoje se je iz izhodiščih 334,7 ± 87,7 m podaljšala na 348,5 ± 89,1 m po 3 mesecih (p = 0,002), 373,2 ± 74,4 m po 6 mesecih (p = 0,005), 383,2 ± 6,3 m po 12 mesecih (p = 0,017) in 396,3 ± 92,8 m po 24 mesecih zdravljenja. Pri zdravljenju nismo ugotavljali pomembnih stranskih učinkov.

Zaključki: Specifična zdravila za zdravljenje pljučne arterijske hipertenzije imajo ugoden učinek pri bolnikih s prirojenimi srčnimi napakami. Pomembno se izbojša telesna zmogljivost. Zdravljenje ni povezano s pomembnimi stranskimi učinki.

Abstract

Background: Pulmonary arterial hypertension with Eisenmenger syndrome as its most advanced form is an important complication of congenital heart disease. In the recent years, advanced therapy for pulmonary arterial hypertension has been introduced. Efficacy and safety of the advanced therapy in our patients with pulmonary arterial hypertension associated with congenital heart disease were analyzed.

Methods: We have analyzed the results of advanced therapy for pulmonary arterial hypertension in patients treated between November 2007 and December 2011. Clinical status, systemic oxygen saturation measured by systemic pulse oximetry, six-minute walking distance and laboratory parameters were assessed. Results at 3, 6, 12 and 24 months of treatment were compared to baseline parameters.

Results: In the observed period, 23 patients were treated with advanced therapy for pulmonary ar-

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terial hypertension. As a first-line drug bosentan was used in 19 and sildenafil in 4 patients. Due to clinical worsening, a second- and a third-line drug had to be added during the study period in 4 and 1 patient, respectively. Eighteen patients (78.3 %) reported improvement in functional capacity. Two patients (8.6 %) died. The mean six-minute walking distance significantly increased over time from 334.7±87.7 m at baseline to 348.5±89.1 m at 3 months (p=0.002), 373.2±74.4 m at 6 months (p=0.005), 383.2±62.3 m at 12 months (p=0.017) and 396.3±92.8 m at 24 months of treatment. No significant adverse events were reported.

Conclusions: Advanced therapy for pulmonary arterial hypertension is beneficial in patients with congenital heart disease. Significant improvement in exercise capacity is observed. The therapy is safe and no significant adverse events were reported.

Introduction

Approximately 5 to 10 % of patients with congenital heart disease (CHD) develop pulmonary arterial hypertension (PAH), mostly as a complication of congenital heart defects with left-to-right shunt.[1] PAH significantly increases morbidity and mortality in patients with CHD.[1-3] The most advanced form of PAH is known as Eisenmenger syndrome. In Eisenmenger syndrome a reversal of shunt is present, leading to chronic cyanosis and its systemic consequences.[4] It is a multisystem disorder associated with various life-threatening complications, including hemoptysis, syncope, infectious endocarditis, brain abscesses, cerebrovascular events and arrhythmias.[1,5,6] Patients with Eisenmenger syndrome have diminished exercise capacity, quality of life and markedly reduced life expectancy.[2,5,7] Until recently, therapeutic options for patients with Eisenmenger syndrome were limited to palliative measures, which reduce symptoms, but do not improve survival.[5,8,9] In highly selected patients lung or heart-lung transplantation was optional.[8,9] In recent years, tremendous advances in the treatment of PAH were achieved. Three groups of pulmonary vasodilators were developed, representing advanced therapy for PAH: prostanoids, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors.[8,10-13] These drugs also significantly improve exercise capacity, hemodynamics, quality of life and survival in patients with Eisenmenger syndrome.[10-15] Large randomized controlled clinical trials have demonstrated that bosentan, an oral endothelin receptor antagonist, has favorable mid- and long-term effects on exercise capacity as well as on hemodynamic parameters.[10,15] Improved survival has also been shown.[14] Smaller studies have also demonstrated effectiveness of sildenafil, an oral phosphodiesterase-5 inhibitor, on exercise capacity and hemodynamics in patients with Eisenmenger syndrome, although no randomized studies are available.[16] Reports on the use of prostanoids, especially intravenous epoprostenol show favorable effects on exercise capacity and hemodynamics in patients with Eisenmenger syndrome, but the use is associated with possible complications, such as paradoxical embolism due to central line and catheter sepsis.[12,13] Epoprostenol is indicated primarily as a first-line therapy for functional class IV patients, or is used as a combination therapy.[17] Rarely, inhaled prostanoid iloprost is used, usually as a combination therapy.[18] The main disadvantage of inhalation therapy is poor compliance, especially in children, due to frequent inhalations (6–9 times daily) that are required.[19]

The aim of the present study was to evaluate the results of treatment with advanced therapy in our cohort of patients with PAH associated with CHD (PAH-CHD).

Methods

Study subjects

Patients with PAH-CHD are treated at the Department of Cardiology of the University Medical Centre Ljubljana and at the Cardiology Unit of the University Children's Hospital Ljubljana. The results of specific PAH treatment in children and adults that were treated between November 2007 and

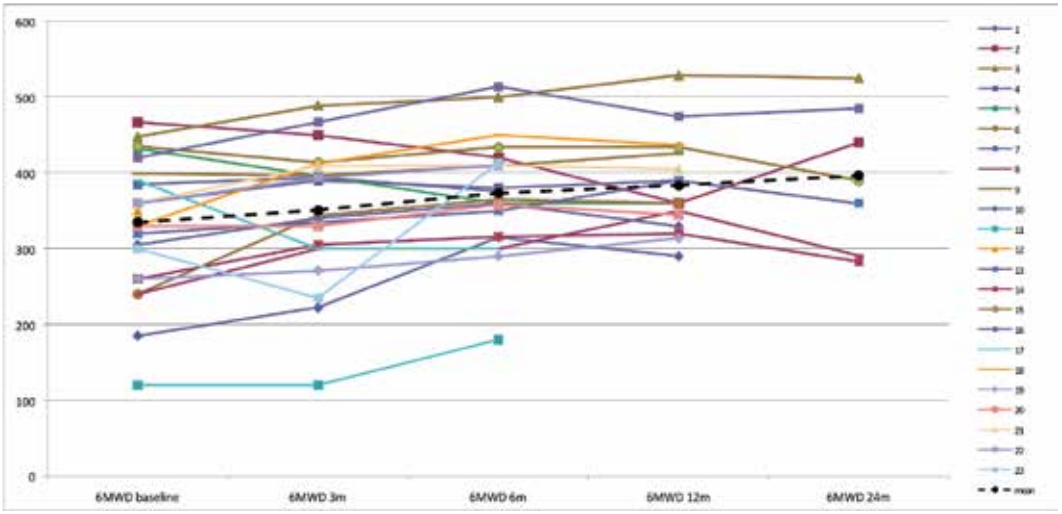

Figure 1: Changes in six-minute walking distance (in m) for individual patient at follow-up.

December 2011 were analyzed retrospectively. Following clinical examination, the diagnosis of PAH-CHD in all patients was confirmed by echocardiography and in the majority of them consequently also by cardiac catheterization. Prior to the introduction of therapy, clinical examination, NYHA functional class, systemic oxygen saturation measured by systemic pulse oximetry and six-minute walking distance (6MWD) were assessed. Laboratory examination included hemoglobin level, liver enzymes and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels. Patients were initially treated with either bosentan or sildenafil. Bosentan was started at 62.5 mg bid in adults. After 4 weeks the dose was uptitrated to maximum 125 mg bid if the patient tolerated the drug well and liver aminotransferase levels remained normal. Dosing in children was modified according to the actual body weight. The dose of sildenafil was 20 mg tid. In case of clinical worsening, an additional therapy was introduced. Patients were followed periodically at 1, 3, 6, 12 months and if stable, yearly thereafter. At follow-up clinical examination, NYHA functional class, oxygen saturation and 6MWD were assessed. Periodical laboratory examination included hemoglobin, liver enzymes and NT-proBNP levels. All patients treated with bosentan had liver enzyme levels controlled monthly.

Table 1: Baseline clinical and functional characteristics of patients.

Characteristic	23 patients
Male, n (%)	7 (30.4%)
Age (years)	24.3±13.2
Body weight (kg)	50.5±18.2
Type of the defect, n (%) ► VSD ► PDA ► ASD ► Complex defects ► Repaired PDA	 4 (17.4%) 2 (8.7%) 1 (4.3%) 15 (65.3%) 1 (4.3%)
Trisomy 21 (Down syndrome)	8 (34.8%)
Baseline hemoglobin level (g/L)	197.5±32.2
Baseline systemic pulse oxymetry (%)	82.9±9.6
Baseline 6MWD (m)	334.7±87.7
Baseline NT-proBNP (ng/L)	1220.9±1874.5

PDA – persistent ductus arteriosus; VSD – ventricular septal defect; ASD – atrial septal defect; 6MWD – 6-minute walking distance; NT-proBNP – N-terminal pro-brain natriuretic peptide

Statistical analysis

Numerical variables were tested for normal distribution and are presented as mean ± standard deviation. Categorical variables are presented as percentage. Repeated measures general linear model (GLM) with Bonferroni's multiple comparisons test was used to assess possible significance of changes in parameter at successive time points. Parameters at 1st month were not included in the analysis. P value < 0.05 was considered statistically significant. Statistical analyses were performed with the SPSS software package (version 18.0).

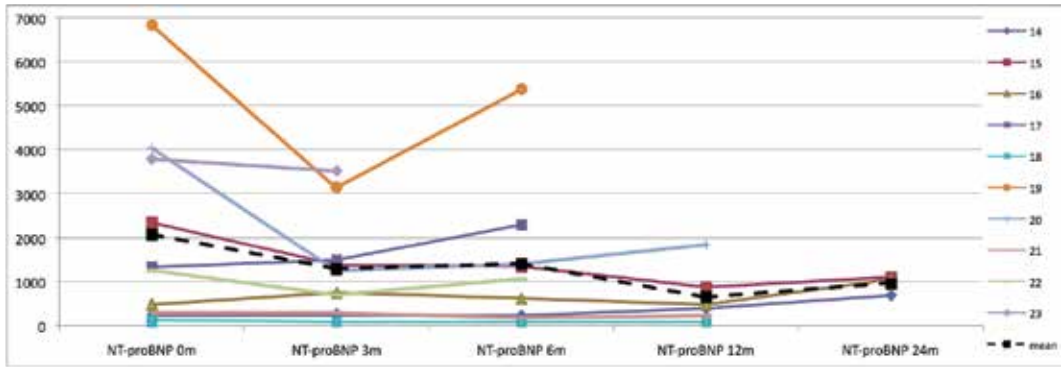

Figure 2: Changes in NT-proBNP levels (in ng/L) for individual adult patient at follow-up. *NT-proBNP – N-terminal pro-brain natriuretic peptide*

NT-proBNP – N-terminal pro-brain natriuretic peptide

Results

In the period of four years, 23 patients were treated with PAH specific therapy. Of these, 7 patients (30.4 %) were male. The mean age at introduction of the therapy was 24.4±13.2 years (range 6.8 to 51.1 years).

Baseline characteristics

The baseline characteristics are shown in Table 1. Simple congenital heart defects were present in 8 patients (34.8 %). Of 15 patients with complex congenital heart defects 6 patients had atrioventricular septal defect (AVSD), 3 patients had double outlet right ventricle with ventricular septal defect (VSD), 2 patients had pulmonary atresia with VSD, 2 tricuspid atresia, and the remaining 2 patients had transposition of the great arteries with VSD and AVSD with pulmonary atresia, respectively. In terms of cardiac surgery, 18 patients were naive. Palliative surgery was performed in 4 patients (17.4 %). One patient presented with severe PAH with right ventricular failure 17 years after complete surgical correction of persistent ductus arteriosus at the age of 2. Down syndrome was present in 34.8 %. All patients were in NYHA functional class III. Two patients have had syncope and another two hemoptysis before the introduction of the therapy.

All patients were assessed by echocardiography. Cardiac catheterization was performed in 17 patients (74 %). The mean pulmonary arterial pressure measured invasively at the time of diagnosis was 69.5±16.2 mmHg.

Treatment regimen

Among 23 patients who received advanced therapy, 19 patients (83 %) were started on bosentan and the remaining 4 patients (17 %) were started on sildenafil. One of the patients who started on bosentan had previously been receiving sildenafil for 5 years. Due to clinical worsening, 4 patients (17 %) were given a combination therapy: 3 patients received bosentan and sildenafil, and the remaining one received bosentan, sildenafil and inhaled iloprost.

Clinical worsening

The mean duration of the therapy was 23.3 months (range 3–49 months). During this period 5 patients were hospitalized: 2 patients had pneumonia, 1 patient had paroxysm of supraventricular tachycardia, 1 patient had brain abscess and the remaining one had worsening of heart failure. Two patients (8.6 %) died. A 27-year-old male patient with tricuspid atresia and amiodarone-induced thyrotoxicosis died suddenly during sleep 3 months after initiation of bosentan. A 22-years-old female patient with surgically corrected persistent ductus arteriosus and postoperative PAH died due to end-stage heart failure 9 months after initiation of the advanced therapy. She was treated with bosentan, sildenafil and iloprost.

Exercise and functional capacity

The mean 6MWD increased significantly over time from 334.7±87.7 m at baseline to 348.5±89.1 m at 3 months (p=0.002),

373.2±74.4 m at 6 months (p=0.005), 383.2±62.3 m at 12 months (p=0.017) and 396.3±92.8 m at 24 months of treatment. Figure 1 demonstrates changes in 6MWD for individual patients.

Eighteen patients (78.3 %) reported an improvement in functional capacity, while 3 patients (13.0 %) did not report any improvement and the remaining 2 patients (8.7 %) could not decide on subjective changes in exercise capacity. One of two patients who died reported progressive worsening.

NT-proBNP

The mean baseline NT-proBNP level was elevated (1220.9 ± 1874.5 ng/L) and was higher in adults than in children (2070.7 ± 2196.9 ng/L vs. 158.6 ± 82.0 ng/L). Changes in NT-proBNP over timer were followed only in adult patients. The mean NT-proBNP levels decreased over time, however changes were not statistically significant (Figure 2).

Safety

All patients tolerated therapy well and no side effects requiring discontinuation of the therapy were observed. No significant changes in pulse, systemic blood pressure or oxygen saturation were observed. Also hemoglobin levels did not change significantly and no significant increase in liver aminotransferases was reported.

Discussion

Patients with Eisenmenger syndrome have high morbidity and mortality.[5,7] The advanced therapy has been demonstrated to improve exercise capacity and decrease morbidity both in children and adults.[10-13,15,16,19] The survival benefit has also been demonstrated.[14] Until recently, bosentan was the only drug approved for the treatment of Eisenmenger patients, but reports on the use of other drugs as well as combination therapy have shown favourable results.[17] Drugs from all the three groups of pulmonary vasodilators are available in Slovenia. The type of drug is selected at PAH-CHD expert-group meeting for each patient individually.

The majority of patients in our series were treated with bosentan. Sildenafil was used as a first-line therapy in patients with elevated liver enzymes or in less compliant patients to avoid frequent controls of liver enzymes due to possible hepatotoxicity of bosentan. Sildenafil was used also as an add-on therapy in patients who demonstrated clinical worsening despite monotherapy with bosentan. Due to progressive right heart failure one patient required triple therapy.

At commencing the therapy, all patients were in NHYA functional class III. The majority of patients (78.3 %) reported an improvement in functional capacity with treatment. This has also been shown for exercise capacity, measured by 6MWD. We have observed a progressive improvement in 6MWD over time, the net increase of mean 6MWD at 24 months was 61.6 m. These results are comparable to other studies, which have shown an increase in 6MWD on advanced therapy.[10-13,15,16,19] Of particular interest is that a significant improvement in exercise capacity in a series as a whole was observed despite the fact that one third of patients had Down syndrome in whom compliance to perform exercise testing is challenging. During the study period, one patient died due to deterioration of heart failure. This patient had corrective cardiac surgery in childhood but had developed postoperative PAH. Patients who develop PAH after complete correction of heart defects are considered the highest risk for complications among PAH-CHD patients and have the poorest outcome.[20] One patient died suddenly during sleep, probably due to arrhythmia. He had concomitant amiodarone-induced thyrotoxicosis, which might have contributed to the fatal outcome.

Baseline NT-proBNP levels were expectedly higher in adult patients as the disease is in a more advanced stage in adults than in children. The advanced therapy has shown a favourable effect on NT-proBNP levels in adults, which have decreased over time. The changes were not statistically significant, however the number of patients was small.

No significant adverse events related to advance therapy were observed. The therapy was well tolerated and no discontinua-

tion was required. In patients on bosentan no increase in liver enzymes was observed, however, due to reported elevations of liver transaminases monthly monitoring of liver enzymes is still required.

Study limitations

The study is retrospective and uncontrolled. The observation period was not the same for all patients; therefore, a longer follow-up period in all the patients might show additional benefit of the treatment. The group is small and heterogenous (including simple and complex CHD, Down syndrome) which might have effect on the response to treatment. Hemodynamic parameters (pulmonary and systemic pressures and resistance) were not evaluated and therefore the effects on these parameters are not reported.

Conclusion

Advanced therapy for PAH has a favourable short- and long-term effect in patients with PAH-CHD. Patients demonstrated improvement in exercise capacity and quality of life. The therapy is well tolerated and no significant side-effects were observed. Due to clear benefits of advanced therapy for PAH, all patients with CHD-PAH should be referred to a specialized centre with expertise in both PAH and CHD. Thorough evaluation of the patients should be performed and advanced therapy should be commenced when indicated.

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