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Rare diseases of pulmonary circulation

Effect of first-month specific therapy determines long-term clinical outcome in patients with pulmonary arterial hypertension (RCD code: II-1A.4.o)

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Abstract

Background: Efficacy of pulmonary arterial hypertension (PAH)-specific therapy may differ among the patients depending on the PAH aetiology. **Aim:** To compare the real-life efficacy of PAH-specific therapy between non-congenital heart disease (non-CHD) and CHD groups of PAH patients and to determine whether an early clinical response has an impact on prognosis. **Methods:** Clinical data from 41 PAH patients, 21 non-CHD and 20 CHD patients, were included in the study. The WHO functional class (WHO-FC), 6-minute walk distance (6MWD) and NT-proBNP serum level were compared at baseline and after 1 and 7 months of PAH-specific treatment. Only patients with unmodified PAH-specific therapy during 7-month follow-up were enrolled in the study. **Results:** Baseline characteristics revealed higher WHO-FC and increased [$\log_e$]NT-proBNP levels (7.74 ±1.05 vs 6.51 ±1.48; p = 0.008) in non-CHD vs. CHD patients; baseline 6MWD was similar in both groups (283.3 ±148.5 m vs 339.2 ±114.7 m). Clinical improvement by at least one WHO-FC after 1-month treatment was observed more frequently in non-CHD (55%) when compared with CHD patients (25%, p = 0.04) and was comparable (50% vs 50%) after 7-month observation. Non-CHD patients, who did not improve within 1 month of treatment were unlikely to achieve improvement after 7 months. The 6MWD increased during the first month of treatment in non-CHD (p=0.009) and in CHD patients (p=0.006) when compared to baseline values and remained at this level after 7 months of treatment. [Log_e]NT-proBNP levels markedly declined only in non-CHD patients, who had an improvement in WHO-FC (8.0 ±1.0 vs 7.4 ±1.1, p = 0.04) in the first month. In CHD patients, the decrease in [$\log_e$]NT-proBNP level was seen (6.5 ± 1.5 vs 6.1 ±1.5, p = 0.04) only within a 1-month observation. **Conclusion:** Efficacy of 1-month PAH-specific therapy is aetiology-dependent and determines clinical outcome in patients with PAH. JRCD 2018; 3 (6): 198–203

Key words: rare disease, congenital heart disease, 6-minute walk distance, targeted therapy

Background

Pulmonary arterial hypertension (PAH) is a progressive disease with multiple aetiologies [1]. PAH-specific therapy with regular monitoring of patients with PAH is strongly recommended by the European Society of Cardiology and European Respiratory Society. There are several clinical parameters such as World Health Organisation Functional Class (WHO-FC), 6-minute walk distance (6MWD), serum level of N-terminal pro brain natriuretic peptide (NT-proBNP) and presence of pericardial effusion, that should be repeatedly evaluated in PAH patients, because of their usefulness in assessing the response to targeted treatment [1]. However, these guidelines are based mostly on observations of patients with idiopathic PAH (IPAH) and may not apply to patients with congenital heart diseases (CHD) [2]. Recently pub-

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Table 1. Baseline characteristic and comparison between CHD and non-CHD groups

Variable	All patients (n = 41)	non-CHD group (n = 21)	CHD group (n = 20)	p
Age [years]	50 ±18	54 ±14	45 ±20	0.09
Female sex (n)	28 (68.3%)	15 (71.4%)	13 (65%)	NS
FC II (n)	5 (12.2%)	1 (5%)	4 (20%)	0.03
FC III (n)	22 (53.7%)	9 (43%)	13 (65%)	
FC IV (n)	14 (34.1%)	11 (52%)	3 (15%)	
6MWT distance [m]	312.7 ±133.0	283.3 ±148.5	339.2 ±114.7	NS
NT-proBNP [pg/ml]	2729.27 ±4778.88 (20 – 27 232)	4125.5 ±6472.88 (397 – 27 232)	1410.6 ±1565.7 (20 – 5450)	0.02
[Log_e]NT-proBNP	7.1 ±1.4	7.74 ±1.05	6.51 ±1.48	0.008
PAH specific theraphy				
Sildenafil (n)	12 (29.3%)	9 (42.8%)	3 (15%)	0.09
Bosentan (n)	23 (56.1%)	6 (28.6%)	17 (85%)	<0.001
Iloprost (n)	6 (14.6%)	6 (28.6%)	0	0.03

CHD – congenital heart disease, FC – functional class, 6MWT – six minute walking test, NT-proBNP – n-terminal pro b-type natriuretic peptide, PAH – pulmonary arterial hypertension

lished studies suggest that escalation of PAH treatment should be provided in the first 4–6 months of therapy [3, 4, 5]. The purpose of our study was to compare the real-life efficacy of PAH-specific therapy in the 1st and 7th months of treatment between non-CHD and CHD groups of PAH patients and to determine whether early clinical response has an impact on prognosis.

Methods

Study population

Forty-one patients, hospitalized between 2009 and 2016 in the First Chair Department of Cardiology, Medical University of Silesia in Katowice, Poland, were retrospectively analysed in this study. All patients were enrolled in a PAH-specific therapy program managed by the Polish National Health Fund. Only patients with unmodified PAH-specific therapy during the 7-month follow-up were enrolled in the study.

The study group consisted of 41 patients with PAH:

- 21 (51%) patients without CHD (non-CHD group; F/M: 15/6): 12 with idiopathic PAH, 8 with connective tissue disease (CTD) and one patient had PAH associated with portal hypertension
- 20 (49%) patients with PAH associated with congenital heart disease (CHD group; F/M: 13/7, including 5 patients with Down Syndrome, F/M: 3/2).

Baseline and follow-up clinical assessment

Baseline assessment was performed before the implementation of PAH-specific therapy. PAH was diagnosed on the basis of right heart catheterisation (RHC) in the non-CHD group. Mean pulmonary artery pressure in the non-CHD group was 62 ±16.4 mm Hg. RHC was not performed on patients with Eisenmenger's syndrome. The following parameters were analysed as indices of clinical improvement: WHO-FC, 6MWD, and serum NT-proBNP level. These were assessed at each follow-up visit and compared to baseline results. Follow-up visits were scheduled for 1 month (1.2 ±0.6 months) and 7 months (7.3 ±1.6 months) after administration of PAH-specific treatment. Clinical outcomes including death or re-hospitalization were determined at the 7-month follow-up. Baseline clinical characteristics including the administered PAH-specific therapy are shown in Table 1.

Statistical analysis

All statistical analyses were performed using Statistica 12. All values are expressed as mean ± standard deviation for continuous variables and number or percentage of subjects for categorical variables. Because of a wide range of NT-proBNP levels, data was compared as log-transformed values to normalize the distribution. The normality of data was verified with the Shapiro-Wilk test. Comparison between unpaired normally distributed samples was performed using Student's t test, while non-normal data was compared with the Mann-Whitney U test. Differences in categorical variables were assessed using the chi-squared test. Changes in normally distributed parameters after the 1st and 7th month of therapy were analysed with paired two samples t-test and the Wilcoxon signed-rank test was used for non-normal distributed data. The strength of correlation between two variables was tested with Spearman's rank correlation coefficient. A p value of < 0.05 was considered statistically significant.

Table 2. Percentage of patients classified in particular WHO-FC in consecutive hospitalizations. p* -comparison of baseline and 1-month assessment; p# – comparison of 1-month and 7-month assessment

	Baseline assessment		1-month assessment		7-month assessment		p*		p#	
	non-CHD	CHD	non-CHD	CHD	non-CHD	CHD	non-CHD	CHD	non-CHD	CHD
	n=21	n = 20	n = 20	n = 20	n=18	n=18				
WHO-FC%										
II	4.8	20	35	30	22.2	44.4				
III	42.8	65	35	65	44.4	44.4	0.02	NS	NS	NS
IV	52.4	15	30	5	22.2	5.6				
Death	-	-	-	-	11.1	5.6				
Improvement at least of one WHO-FC%			55	25	50	50				
p non-CHD vs CHD			0.04		NS					

Results

Baseline assessment

Comparison of WHO-FC between non-CHD (5% in FC II, 43% in FC III, and 52% in FC IV) and CHD (20% in FC II, 65% in FC III, and 15% in FC IV) groups revealed a more advanced baseline clinical PAH presentation in non-CHD patients (p = 0.03).

The 6MWD was similar in both groups (283.3 ±148.5 m vs 339.2 ±114.65 m, p = NS) (Table 1).

[Log_e]NT-proBNP level was significantly higher in the non-CHD group than in the CHD-group (7.74 ±1.05 vs 6.51 ±1.48; p = 0.008).

The 6MWD correlated with WHO-FC in the non-CHD group (R = -0.54, p = 0.02), but not in CHD patients (R = -0.30; p =x0.2).

1-month assessment

Improvement by at least one WHO-FC was observed in 11 (55%) patients from the non-CHD group and in 5 (25%) patients from the CHD-group (p = 0.04) (Table 2). The majority of CHD patients [13 (65%)] remained unchanged in contrast to the non-CHD-group [7 (35%), p = 0.04]. The same percentage of patients [2 (10%)] worsened in both groups.

The 6MWD increased significantly in both the non-CHD (p = 0.009) and CHD groups (p = 0.006) (Table 3). There was no significant difference in the change of 6MWD between the non-CHD and CHD groups (p = 0.33).

There was a significant difference in [log_e]NT-proBNP levels between non-CHD and CHD groups (7.4 ±1.07 vs 6.15 ±1.46; p <0.001). [Log_e]NT-proBNP value noticeably decreased in non-CHD patients who had an improvement in WHO-FC (8.0 ±1,0 at baseline vs 7.4 ±1.1 in first month, p = 0.04) and remained unchanged when no improvement was observed (7.1 ±0.6 at baseline vs 7.4 ±0.9 in first month; NS). In CHD patients, the decrease in [log_e]NT-proBNP level was significant (6.5 ±1.5 vs 6.1 ±1.5, p = 0.04).

6MWD correlated with WHO-FC (R = -0.62, p = 0.006) and [log_e]NT-proBNP value (R = -0.50, p = 0.04) only in the non-CHD group.

7-month assessment

7-month follow-up

Data from the 7-month-follow-up was available for 18 (85.7%) patients from the non-CHD group and 18 (90%) patients from the CHD group. A total of 5 patients, 3 (14.3%) non-CHD and 2 (10%) CHD, did not attend their follow-up visit but were still alive. Two (9.5%) out of 21 patients from the non-CHD group and 1 (5%) out of 20 patients from the CHD group died between the 1st and 7th month of treatment.

7-month assessment

Improvement by at least one WHO-FC was observed in 50% of patients both in the non-CHD and CHD groups (Table 2). WHO-FC remained unchanged when compared with data from the 1-month assessment.

The majority of non-CHD patients (87.5%) maintained improvement for 1 month after another 6 months of therapy and only 1 patient, who did not respond to treatment in the first month, achieved improvement after 7 months. Comparing the 7th month WHO-FC to the 1st month WHO-FC, 83.3% of CHD patients had a sustained improvement and another 4 patients had a decreased WHO-FC compared to baseline and the 1 month assessment.

The 6MWD increased when compared with baseline observations and did not differ from the 1-month assessment in both groups (Table 3).

There was a significant difference in [log_e]NT-proBNP levels between non-CHD and CHD groups (p = 0.02) (Table 4). [Log_e]NT-proBNP levels tended to be lower in patients who improved (7.8 ±1.0 at baseline vs 6.8 ±1.5 in the 7th month; p = 0.09) and were stable in patients without improvement (7.1 ±0.7 at baseline vs 8.0 ±1.5 in the 7th month; p = 0.16). There was no difference in [loge]NT-proBNP values in CHD-patients (6.6 ±1.5 at baseline vs 6.33 ±1.29 in the 7th month; p = 0.3). This applied to patients who experienced improvement as well as patients who did not.

Table 3. Evaluation of 6MWT distance changes in consecutive hospitalization. * comparison of baseline and 1-month assessment; # comparison of 1-month and 7-month assessment;%Δ 6MWT=(follow-up 6MWT – baseline 6MWT)/ baseline 6MWTD × 100%

	Baseline assessment		1-month assessment		7-month assessment		p*		p#	
	non-CHD	CHD	non-CHD	CHD	non-CHD	CHD	non-CHD	CHD	non-CHD	CHD
	n = 18	n = 20	n = 18	n = 20	n = 13	n = 17				
6 MWT distance (m)	283.3 ±148.5	339.2 ±114.7	359.8 ±103.8	377.3 ±106.1	345.7 ±90.2	380.7 ±110	**0.009**	**0.006**	NS	NS
p non-CHD vs CHD	NS		NS		NS					
%Δ 6MWT (%)			27.0	11.2	37.0	12.4				
p non-CHD vs CHD			NS		NS					

Inverse correlations between 6MWD and WHO-FC (R = -0.65, p = 0.02), and between 6MWD and [loge]NTpro-BNP (R = -0.61, p = 0.02) were observed in the non-CHD group.

Discussion

The main finding of our study concerns the real-life efficacy of PAH-specific therapy in CHD and non-CHD patients. Clinical improvement by at least one WHO-FC after a 1-month treatment was observed more frequently in non-CHD when compared with CHD patients. Moreover, we determined that the efficacy of a 1-month PAH-specific therapy was aetiology-dependent and influenced clinical outcome in patients with PAH. The first month of PAH-specific treatment was crucial for non-CHD patients. In this group, those who did not improve within 1 month of treatment initiation were unlikely to achieve improvement in the next 7 months. CHD patients responded to PAH-specific treatment gradually and steadily during the 7-month observation period. Finally, a significant improvement in WHO-FC was observed in half of the non-CHD and CHD patients after a treatment period of 7 months.

Previously, early improvement in WHO-FC to class I or II was considered as a prognostic factor for long-term survival [6, 7]. Recently, several studies of PAH were published [3, 4, 5]. In these studies, follow-up assessment was useful for further prognosis. In French [3] and Swedish [4] studies, early response to therapy, assessed approximately 4 months after implementation of PAH-specific treatment, improved long-term prognosis. Those results highlight the importance of our findings that the first month of treatment is crucial in non-CHD patients. In our study, a positive response to therapy in the first month was a predictor of 7-month improvement in this group. It was unlikely for non-CHD patients to achieve improvement after 7 months if they did not respond to treatment in the first month. Escalation of PAH-specific therapy after an unsuccessful first month should be considered. Conversely, CHD patients, who did not respond to treatment in the first month still showed an improvement after 7 months of therapy.

Another parameter we were interested in was the 6MWD. This increased in both groups significantly during the first month of assessment when compared to the baseline distance and remained unchanged during the next 6 months of observation. The 6MWD also correlated strongly with WHO-FC and moderately with [$\log_e$] NT-proBNP in the non-CHD group during subsequent hospitalization, which demonstrates its usefulness as an objective parameter to assess efficiency of PAH-specific therapy in this group. Surprisingly, even though WHO-FC and 6MWD also improved in the CHD group, there was a weak correlation between these parameters. Furthermore, no relationship between 6MWD and [$\log_e$] NT-proBNP in the CHD group was observed. We should focus on co-morbidities such as genetic or orthopaedic disorders [8], which may not allow such patients to achieve the expected distance corresponding to their WHO-FC. On the other hand, the young age of CHD-patients may allow them to cover a greater distance than expected according to their FC. The importance of NT-proBNP as an improvement parameter in the CHD group is unclear in our study. It may be associated with a limited number of patients and relatively lower NT-proBNP levels in CHD subjects.

The results of our study on the efficiency of PAH-specific therapy correspond well to several placebo-controlled trials in non-CHD and CHD patients. Analyses of bosentan therapy effectiveness in patients with IPAH or PAH associated with scleroderma [9, 10] and sildenafil therapy in non-CHD and CHD patients [11] demonstrated a similar WHO-FC improvement (42–43%) and an increase in 6MWD by 36 – 70 meters in 12–16 weeks. Moreover, analysis of iloprost effectiveness in PAH treatment [12] is in line with the above results. Another finding from our study was a strong correlation between the 6MWD and WHO-FC in the non-CHD group. Another study demonstrated a significantly decreased 6MWD, which was proportional to the severity of the WHO-FC in IPAH [13].

Bosentan is recommended by the European Society of Cardiology as an initial treatment in WHO-FC III patients with Eisenmenger's syndrome [1, 14], although further randomized clinical trials are needed. Bosentan has been shown to improve 6MWD after 16 weeks of treatment among CHD patients with WHO-FC III [15], which is in line with our observations. In contrast to our findings, a study on combined therapy with bosentan and sildenafil in the treatment of Eisenmenger's syndrome [16] revealed a strong correlation between increased 6MWD and decreased serum NT-proBNP level.

Table 4. Evaluation of [loge]NT-proBNP changes in consecutive hospitalization.. * comparison of baseline and 1-month assessment; # comparison of 1-month and 7-month assessment;%Δ[loge]NT-proBNP =(follow-up [loge]NT-proBNP – baseline [loge]NT-proBNP)/baseline [loge]NT-proBNP × 100%

	Baseline assessment		1-month assessment		7-month assessment		p*		p#	
	non-CHD	CHD	non-CHD	CHD	non-CHD	CHD	non-CHD	CHD	non-CHD	CHD
	n=17	n = 16	n = 17	n = 16	n=13	n=14				
[loge]NT-proBNP	7.74 ±1.05	6.51 ±1.48	7.4 ±1.07	6.15 ±1.46	7.27 ±1.57	6.33 ±1.29	NS	0.04	NS	NS
p non-CHD vs CHD	**0.008**		**<0.001**		**0.02**					
%Δ [$\log_e$]NT-proBNP (%)			4.39	5.53	3.45	3.65				
p non-CHD vs CHD			NS		NS					

We also observed a significant difference in the serum NT-proBNP level between non-CHD and CHD patients, which was noticeable before the implementation of PAH-specific therapy as well as in the follow-up. Non-CHD patients tended to have higher serum NT-proBNP level than CHD patients.

A significant correlation between clinical improvement and NT-proBNP was described for IPAH as well. According to analysis in this group of patients, WHO-FC significantly correlated with 6MWD, NT-proBNP, and haemodynamic parameters [17]. Based on this data, NT-proBNP is accepted as an marker in IPAH [18].

When comparing the above data to our observations, there was no significant correlation between WHO-FC improvement and NT-proBNP decrease in CHD patients. Further analysis on a larger group of patients is required.

Based on the outcomes of our study, we believe that early escalation of therapy in patients with PAH may be beneficial in case of inefective one-month treatment, especially in the non-CHD group.

Limitation of the study

The main limitation of our study was the small number of patients. Additionally, our study was retrospective and took into account data from only a single-centre. To analyse efficacy of PAH-specific therapy, we used only simple indices of clinical improvement. We were unable to determine whether early escalation of PAH-specific treatment would improve WHO-FC in a 7-month observation, because only patients with unmodified PAH-specific treatment in the 7-month follow-up were enrolled in the study.

We did not analyse changes in echocardiographic parameters because of the diversity of data regarding non-CHD and CHD patients in our study population.

Finally, our study was not designed to evaluate the long-term effects of therapy or to demonstrate improved survival outcomes associated with therapy.

Conclusion

Efficacy of 1-month PAH-specific therapy is aetiology-dependent and determines clinical outcome in patients with PAH. Response to the first month of PAH-specific treatment is crucial in non-CHD patients, as it determines clinical condition in further months. CHD patients respond to PAH-specific treatment gradually and steadily during the 7-month observation. The outcomes of our study demonstrate, that early escalation of therapy in PAH may be beneficial, especially in non-CHD patients.

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