TREATMENT OPTIMALIZATION IN PEDIATRIC PULMONARY HYPERTENSION

PhD thesis

László Ablonczy

Károly Rácz Doctoral School of Clinical Medicine

Semmelweis University

Supervisor: György Reusz, MD, PhD, DSc

Official reviewers: Anikó Bohács, MD, PhD

Judit Barta, MD, PhD

Head of the Complex Examination Committee: László Szabó, MD, PhD

Members of the Complex Examination Committee:

László Wágner, MD, PhD

Gábor Mogyorósy, MD, PhD

Budapest

2022

1. Introduction

Pulmonary hypertension (PH) is a rare disease with poor prognosis and diverse etiology in pediatric patients. With a few specific exceptions (such as PH associated with bronchopulmonary dysplasia (BPD) or congenital diaphragmatic hernia), the course is similar, with progressive damage to the pulmonary vasculature, which is irreversible in the majority of cases. However, the dynamics of the disease may vary depending on the etiology, so proper diagnosis is as important as personalised treatment. In addition to non-invasive diagnostics, invasive hemodynamic testing is of particular importance, because the hemodynamic definition is used to confirm the diagnosis of the disease. Once the diagnosis of PH is confirmed, therapeutic options can be decided.

The etiology is of prognostic importance for the survival of patients with pulmonary hypertension and therefore influences the therapy. In addition to the etiology, several risk factors determining prognosis have been identified in recent years. The risk stratification proposed by the international guideline, which has been introduced mainly for the idiopathic form, defines high and low values of the risk factors in childhood and examines the presence of a given risk factor, which then forms the basis for the choice of therapy.

The main PAH-specific drugs used in children are endothelin receptor antagonists (ERAs), phosphodiesterase 5 inhibitors (PDE5i) and prostacyclin analogues. In the low-risk group, oral PAH-specific therapy is recommended (PDE5i and ERA), mostly in combination. In high-risk cases, parenteral prostacyclin is recommended subcutaneously or intravenously as monotherapy or as part of a combination regimen.

2. Objectives

In Hungary, the Pediatric Heart Center of Gottsegen National Cardiovascular Center is dedicated for pediatric cardiology and pediatric cardiac surgery. Our centre started specialised treatment of PH patients 20 years ago and since then we have treated nearly 160 children. We currently treat 50-60 patients for PH every year. After a systematic review of risk assessment, treatment outcomes and quality of life, we set the following goals:

2.1. To determine the prognostic value of early risk stratification in pediatric PH

- 2.1.1. Impact of etiology on prognosis
- 2.1.2. Significance of different risk factors, the number of risk factors
- 2.1.3. Evaluation of hemodynamic risk factors for transplant-free survival

2.2. Analysis of our pediatric experience of subcutaneous treprostinil treatment as part of advanced PAH treatment

- 2.2.1. Assessment of tolerability of subcutaneous treprostinil therapy in children
- 2.2.2. Study of disease progression in children treated with subcutaneous treprostinil
- 2.2.3. Dose-titration and target dose achievement rate

2.3. To assess QoL in our PH patient population

- 2.3.1 Comparison of iPAH and CHD in terms of QoL
- 2.3.2 Investigation of the association between age and QoL
- 2.3.3 Examination of PAH risk factors in terms of QoL

All of the following studies were performed in accordance with the Declaration of Helsinki
(ethical permissions: SE RKEB numbers 125/2020, 127/2020)

3. Methods

3.1 Risk stratification study

The database of 58 pediatric PH patients (aged 0.1-16 years at time of diagnosis, median 4.2 years, 29 male) treated between 1995 and 2019 at our centre was reviewed retrospectively. PH patients were classified according to Rosenzweig et al. Out of 58 PH patients, 12 patients had iPAH (group 1.1), 32 patients had PAH associated with congenital heart disease (CHD) (group 1.4.4), 2 patients had connective tissue disease (group 1.4.1), 2 patients had PH associated with lung disease (group 3), and 10 patients had multifactorial PH with complex heart disease (group 5). Due to the lack of initial hemodynamic measurements, PH patients associated with BPD were excluded. The median follow-up time was 5.4 years.

Baseline data collected at the time of diagnosis were demographics, WHO FC, echocardiographic and hemodynamic parameters. Echocardiographic parameters considered as signs of possible PH were RA/RV enlargement, reduced LV size, increased RV/LV ratio, reduced TAPSE, and pericardial effusion. Hemodynamic parameters included mRAP, mPAP, PWCP, and mean arterial pressure. Systemic and pulmonary blood flows, indexed resistances (systemic and pulmonary vascular resistance index - WU*m2) were calculated. Determinants of elevated PH risk were cardiac index < 2.5 L/min/m2 , mRAP> 10 mmHg, PVRI > 20 WU*m2 , and systemic venous

saturation < 60%. NT-ProBNP level testing was not performed routinely at the time of diagnosis. As the median age of our patients was only 4.2 years, the 6-MWT was not performed routinely.

3.2 Subcutaneous treprostinil study

The database of 56 pediatric PH patients treated between 2006 and 2016 in our institute was reviewed retrospectively. From our 56 PH patients, 32 patients had PAH associated with CHD (group 1.4.4), 9 patients had PH associated with lung disease (7 pts with BPD) (group 3), 3 patients had connective tissue disease (group 1.4.1), and 12 patients had iPAH (group 1.1). Exclusion of other causes of PH were conducted according to the guidelines.

During the study period, 8 patients were treated with subcutaneous treprostinil. 7 of 8 patients had iPAH (group 1.1) and 1 had PH associated with pulmonary hypoplasia and complex congenital malformations (group 3).

Basic patient characteristics are listed in **Table 2**.

Table 2. Patient characteristics

Pt	Dg	Age at DG (years)	PVRi at dg (WU*m2)	TR at dg (m/s)	Age at TREin (years)	WHO FC at TREin	NT-proBNP at TREin (pg/ml)
1	iPAH	8.1	8.6	5.0	13.4	III	8042
2	iPAH	13.6	21.2	4.6	14.7	III	3950
3	aPAH	2.4	10.5	4.8	8.4	IV	6900
4	iPAH	10.3	13.8	4.2	11.4	III	2294
5	iPAH	1.4	5.2	4.7	2.6	III	8656
6	iPAH	12.5	17.1	5.4	14.2	IV	not performed
7	iPAH	3.1	15.6	4.6	4.2	IV	19653
8	iPAH	1.9	16.5	5.0	14.3	III	not performed

TREin: treprostinil initiation; WHO FC: TR: tricuspid regurgitation

Baseline data collected at the time of diagnosis and before the initiation of treprostinil were as follows: demographics, WHO FC, serum NT-proBNP levels, echocardiographic parameters and hemodynamic data. Calculated parameters were systemic and pulmonary blood flow and indexed resistances (SVR and PVR in WU*m2). Patients were reexamined at 3 to 6 month intervals, collected data included WHO FC and echocardiogram. NT-proBNP was measured only at time of clinical worsening.

The initial treprostinil dose was 2 ng/kg/min, increasing to 10 ng/kg/min over 5 days. Subsequent dose adjustments were made based on clinical symptoms. Target dose was defined as 60 ng/kg/min. Treprostinil was administered as a continuous subcutaneous infusion via an ambulatory microinfusion pump.

3.3 QoL study

Data of 25 patients (aged 2–18 years, 17 male) with a diagnosis of PH requiring specific medical treatment was reviewed in this cross-sectional study. Of 25 PAH patients according to clinical classification 1 had iPAH (group 1.1), 15 patients had PAH associated with CHD (group 1.4.4), 2 patients had PH associated with lung disease (group 3), 7 patients had multifactorial PH with complex heart disease (group 5).

To assess the PAH patients' health-related quality of life (HR-QL), the validated Hungarian version of the Pediatric Quality of Life Inventory (PedsQL™) 4.0 Generic Core Scales (QL-GCS) and the PedsQL™ 3.0 Cardiac Module (QL-CM) were used. The reference data of the QL-CM summarises the results of the entire cardiological spectrum and it also contains a more detailed breakdown depending on the severity of heart disease.

The QL-GCS has 4 (physical, emotional, social, school functioning), whereas the QL-CM has 6 (heart problems-symptoms, treatment, perceived physical appearance, treatment anxiety, cognitive problems, communication) domains with child self-report and parent proxy-report formats. Child self-report and parent proxy-report includes ages 5-7 years (young child), 8-12 years (child), and 13-18 years (adolescent), the parent survey includes an extra 2-4 years (toddler) format. Patients aged 5–18 years with appropriate mental/cognitive

capacity completed both age specific QL-GCS and QL-CM. The parent report and the self-report questionnaire used a 5-point Likert score (0 = never, 1 = almost never, 2 = sometimes, 3 = often, and 4 = always). It was linearly transformed, resulting in a score of 0–100; higher scores indicating better pediatric quality of life.

In addition, we have calculated Psychosocial Health Summary Score (Psychosocial Sum), where the sum of the Likert scores is divided by the number of questions answered in the Emotional, Social, and School Functioning Modules.

At the time of the study, WHO FC, symptoms of right heart failure, echocardiographic parameters (TAPSE - mm/Z score, left ventricular end-systolic diameter - mm/Z score, left ventricular end-systolic eccentricity index) were available as risk stratification data. NT-proBNP levels were also available in 50% of patients. Hemodynamic measurements were performed within one year in 20% of children. Regarding specific therapy for PAH, 18 patients were on monotherapy, 6 patients were on dual oral therapy and only 1 patient was receiving triple therapy including prostacyclin at the time of the study.

4. Results

4.1. Risk stratification study

The majority of patients were in a stable clinical status at diagnosis (WHO FC I-II 56/58 cases). Clinical signs of right heart failure were more frequent (25/58), mainly in the form of fatigue and exertion complaints. This difference between stable clinical status and the presence of symptoms of right heart failure also shows the difficulty of accurately assessing WHO FC in children.

Growth failure was observed in ¼ of children. The presence of at least 1 of the echocardiographic parameters suggestive of poor prognosis was confirmed in more than half of the patients (35/57, 61.4%). Hemodynamic parameters at time of diagnosis are shown in **Table 4**. At least 1 of the hemodynamic parameters reached a value which could be classified as high risk (CI<2.5 l/min/m2, mRAP>10 mm Hg, PVRi>20 WU*m2, SVO2<60%) in nearly half of the patients (48%).

Table 4. Hemodynamic parameters at the time of diagnosis

Hemodynamic parameters	Value
Cardiac index (l/min/m2)	3.5 (1.3-7.4)
Mean right atrial pressure (mRAP) (mmHg)	9 (3-29)
Systemic venous saturation (%)	68 (30-82)
Pulmonary vascular resistance index (PVRI) (WU*m2)	10.4 (3.7-70.0)

variables are given in median (range)

The average follow-up was 5.4 years, with a mortality rate of 29%. Altogether 33% of patients reached the composite endpoint (death or lung transplant).

In terms of poor outcome, idiopathic and CHD-associated forms were compared, the latter predicting a significantly better prognosis (even after adjusting for age (hazard ratio = 0.12 [95% confidence interval: 0.03-0.48], P = 0.0024) (**Figure 1/a, 1/b**). Presumably due to the low number of cases, neither WHO FC (P = 0.0866), nor clinical signs of right ventricular failure (P

= 0.2760) or developmental delay (P = 0.630) had significant prognostic value in our study.

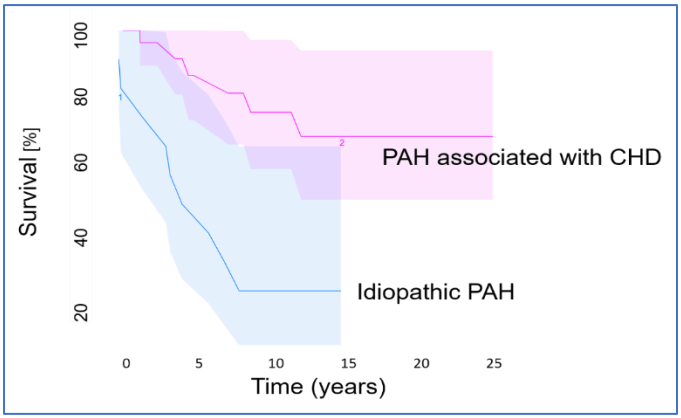

Figure 1/a. Mortality in iPAH (n=12) compared to the patients with CHD associated PAH (n=32)

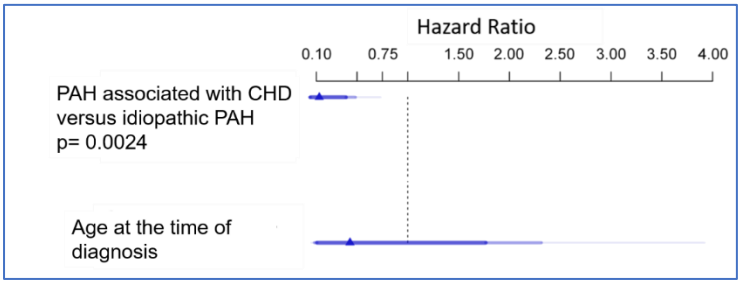

Figure 1/b Multivariate analysis of mortality in patients with CHD associated PAH (n=32) compared to the patients with iPAH (n=12)

Similarly, the echocardiographic parameters were not found to be prognostic determinants (P = 0.0576).

Due to their importance, hemodynamic parameters were analysed separately. First, taking into account the pathological cut-off values defined by the risk stratification, we compared the group of patients with one or more pathological values to children with hemodynamic parameters in the normal range and there were no significant difference between the two groups. Considering PVRi alone as the most important parameter, we found a 49.1% higher hazard ratio for every 10 WU*m2 increase in PVRi (95% confidence interval: 1.13-1.97, P = 0.0048) (**Figure 2**)

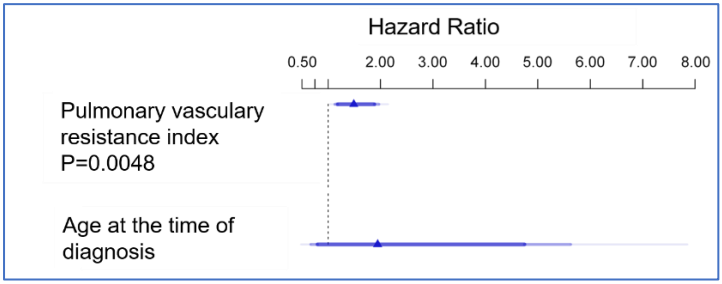

Figure 2. Effect of PVRi on mortality in our pediatric PAH population - multivariate analysis

We also analysed the number of risk factors at the time of diagnosis. We found an average of 2 risk factors, with an average of 2.5 in iPAH patients and an average of 1 in CHD-related PAH. The number of risk factors alone was not associated with worse prognosis in the study population (P=0.1534).

4.2. Treprostinil study

After the above described initiation and titration of subcutaneous treprostinil, patients had their dosage increased to the target level of 60 ng/kg/min

treprostinil (median (range 10-100) ng/kg/min). Two patients died early after treprostinil initiation (one after 3 days and the other after 7 days) due to PAH progression (**Table 5**).

Table 5. Treprostinil therapy characteristics and outcome

iPAH: idiopathic pulmonary arterial hypertension; aPAH: associated pulmonary arterial hypertension; Pt: patient; Dg: diagnosis; TRE: treprostinil; WHO FC: World Health Organization functional class; tx: transplantation; = no change; =* no change, early death; =** no change, early lung transplant;↑ increase in WHO FC; ↓decrease in WHO FC

Pt	Dg	Time on TRE (years)	Final TRE dose ng/kg/min	WHO FC change	Outcome
1	iPAH	1.57	70	=	death on lung tx waiting list
2	iPAH	2.31	60	=	lung tx, survival
3	aPAH	4.31	60	↓	survival
4	iPAH	2.10	100	↑	Potts shunt, lung tx, survival
5	iPAH	0.33	80	=	Potts shunt, death
6	iPAH	0.003	10	=*	death
7	iPAH	0.02	40	=*	death
8	iPAH	0.02	10	=**	lung tx, death

Maximal dose of subcutaneous treprostinil reached 100 ng/kg/min in one patient. The preferred s.c. site was the abdominal wall, even in small children. Subcutaneous set replacement was performed on average 2-3 times per month**.** The most common adverse events were pain and local reactions at the s.c. site, which were managed by s.c. site change and minor analgesics (paracetamol). None of the patients discontinued s.c. treprostinil treatment due to site pain. Potentially due to the small patient number, no correlation was found between the local pain and treprostinil s.c. dose or volume.

Thrombocytopenia was observed on one occasion, at a high treprostinil level (100 ng/kg/min). Thrombocytopenia resolved after decreasing the treprostinil dose. No severe hypotension, nausea, headache, cough or diarrhea were reported.

Seven out of 8 patients reached end stage disease 1.0 year (median, range 0.03-2.4 years) after treprostinil initiation. Four patients suitable for LuTx were put on the waiting list. Three patients had a successful lung transplantation (one after Potts shunt), one died while on the waiting list.

Potts shunt as a palliative surgical technique was performed in two cases. In one patient, who was too young for LuTx, Potts shunt implantation was performed after the ineffective triple combination drug therapy, but without long-term success. In a second patient, Potts shunt was a short (54 days) bridge to successful lung transplantation. perioperatively.

4.3. QoL study

Questionnaires for different age groups were completed by children in the following age distribution: 7 patients in the 2-4 age group, 4 in the 5-7 age group, 8 in the 8-12 age group and 6 in the 13-18 age group. A total of 3 children were unable to complete the questionnaire due to mental health

problems. PedsQL-GM and QL-CM Likert scores according to age are shown in **Table 6**.

Table 6. PedsQL™ Generic Core Scales (PesQL™-GM) and PedsQL™ 3.0 Cardiac Module scores (PedsQL-CM) in our patients

	PedsQL™-GM		PedsQL™-CM	
	self-report	parent proxy-report	self-report	parent proxy-report
Patients aged 2-4 years (n=7)	-	92.3 (52.1-100.0)	-	78.3 (59.1-96.4)
Patients aged 5-7 years (n=4)	72.0 (70.0-100.0)	84.1 (79.6-90.5) (n=3)	82.8 (66.3-100.0) (n=3)	90.5 (75.7-100.0) (n=3)
Patients aged 8-13 years (n=8)	52.7 (41.6-91.4)	57.1 (5.0-89.8)	68.3 (28.8-91.3)	59.3 (34.8-94.3)
Patients aged 13-18 years (n=6)	66.3 (50.2-74.1) (n=3)	63.5 (48.8-71.9) (n=5)	69.0 (46.2-79.3) (n=4)	52.2 (45.4-70.2)

data expressed in median (range) value

Using PedsQL™-GM and CM data from previous studies based on Hungarian general pediatric population and that of children attending a cardiac unit with different type of heart diseases as reference, a compelling difference was found, as PAH patients have significantly lower values than the general

Hungarian pediatric population in every core domain. Further, PAH patients have lower QL-CM scores than patients with different heart diseases in Physical, Emotional, Social, Psychosocial Sum domains and in total scores. Using the detailed break-down of patients with different disease severity, PAH patient's PedsQL-CM scores were similar to those with chronic heart disease with great complexity (**Table 7**).

Table 7. PedsQL™ Generic Core self report scores (PedsQL™-GM) of general Hungarian pediatric population, children with CHD and pts with PAH

	Healthy (n=366)		CHD (n=164)		CHD-with great complexity (n=22)		PAH (n=25)		p values	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	healthy - PAH	CHD - PAH
Physical	83.1	14.2	78.3	18.8	67.8	21.8	63.9	28.6	<0.001	0.003
Emotional	72.1	17.8	71.7	17.1	65.5	20.5	62.9	21.9	<0.001	<0.001
Social	83.8	16.1	82.6	17.5	73.3	17.7	61.8	31.1	<0.001	<0.001
School functioning	75.8	16.7	73.9	16.8	70.9	22.6	64.3	25.8	0.034	NS
Total	79.3	12.3	76.9	14.6	70.5	16.8	62.9	24.5	<0.001	<0.001
Psychosocial Sum	77.3	13.4	76.1	14.5	72.12	17.7	63.9	23.9	0.002	0.006

There was significant negative correlation between patient age and QL-CM parent proxy Likert scores ($r=-0.49$, $p<0.05$) and QL-CM parent proxy Likert scores ($r=-0.58$, $p<0.05$). There was significant positive correlation between

TAPSE Z scores and QL-GCS patient self-report Likert scores ($r=0.46$, $p<0.05$) and parent proxy Likert scores ($r=0.47$, $p<0.05$). In contrast, we found no significant differences in the self-report and parent-proxy Likert scores based on Z-score values of LVIDs and similarly no significant difference was noted based on the left ventricular end-systolic eccentricity index.

There was a significant difference in parent proxy Likert scores between patients with WHO FC I and class II-IV. In addition, patients with WHO FC I had higher QL-GCS parent proxy Likert scores in School Functioning module ($p=0.029$) and QL-CM parent proxy Likert scores in Heart Problems and Symptoms module ($p=0.014$).

When comparing patients with PAH on monotherapy versus combination therapy, no significant difference could be observed in the self-report and parent proxy Likert scores.

5. Conclusions

In our risk stratification study, we clearly confirmed that children treated with CHD-related PAH have a lower mortality risk. In early risk stratification, PVRi was found to be the strongest risk factor for survival, even when adjusted for age. Combined hemodynamic risk factors did not show similar results. Among the other risk factors in our study, WHO functional status was not found to be a significant prognostic factor for survival in early risk stratification, mainly due to the study limitations. In early risk stratification, few parameters showed prognostic value for transplant-free survival, and it is therefore recommended to reassess risk stratification during follow-up on a regular basis.

Of the parenteral prostacyclins, recommended in the high-risk group, the subcutaneous treprostinil we studied, was found to be well tolerated in our

patient population, with dose titration and target dose successfully achieved in the majority of cases. In the iPAH group, all patients reached the composite endpoint within 2.5 years after initiation of parenteral prostacyclin therapy at the latest. This confirms the practice of some centres to start triple therapy including parenteral prostacyclin early (up-front or rapid sequential therapy setup) and to use high doses of prostacyclin in iPAH.

Our QoL study confirmed the hypothesis that pediatric PAH is a serious disease in terms of quality of life, corresponding to the most severe cardiac malformations among heart diseases. Quality of life shows a strong negative correlation with age, which should be taken into account especially in the treatment of adolescents, for the latter, psychological support is of paramount importance. In terms of QoL, we could not prove (the low number of patients in the parenteral prostacyclin group) whether the negative effect of the limitations associated with subcutaneous pump treatment or the positive effect of the improvement in functional status played a more important role. The negative effects of the physical limitation using a subcutaneous treprostinil pump can be reduced with an implantable device. Contrary to the risk stratification study, the QoL study confirmed the important role of TAPSE as a parameter indicating better ventricular function in the follow-up of therapy. Well-treated children are asymptomatic (WHO FC Class I) and have good RV function, and these facts are assumed to result in a better quality of life.

6. Bibliography of the candidate's publications

Publications related to the thesis

1. **Ablonczy L**, Mayer Z, Somoskövi O, Berkes A, Csenteri O, Kis E, Reusz GS. Assessment of quality of life in children with pulmonary hypertension using parent and self-report questionnaires. Transplant Proc. 2022 Nov 15:S0041-1345(22)00721-7.
2. **Ablonczy L**, Ferenci T, Somoskövi O, Osváth R, Reusz GS, Kis E. Prognostic value of early risk stratification in pediatric pulmonary hypertension. Transplant Proc. 2021 Jun;53(5):1439-1442.
3. **Ablonczy L**, Tordas D, Kis E, Szatmári A. Use of subcutaneous treprostinil in pediatric pulmonary arterial hypertension-Bridge-to-transplant or long-term treatment? Pediatr Transplant. 2018 Mar;22(2).

Publications not related to the thesis

1. García Aguilar H, Gorenflo M, Ivy DD, Moledina S, Castaldi B, Ishida H, Cześniewicz P, Kusa J, Miera O, Pattathu J, Weng KP, **Ablonczy L**, Apitz C, Katona M, Kurosaki K, Pulido T, Yamagishi H, Yasuda K, Cisternas G, Goth M, Lippert S, Radomskyj A, Saleh S, Willmann S, Wirsching G, Bonnet D, Beghetti M. Riociguat in children with pulmonary arterial hypertension: The PATENT-CHILD study. Pulm Circ. 2022 Jul 1;12(3):e12133.
2. Laeer S, Cawello W, Burckhardt BB, **Ablonczy L**, Bajcetic M, Breur JMPJ, Dalinghaus M, Male C, de Wildt SN, Breitkreutz J, Faisal M, Keatley-Clarke A, Klingmann I, Lagler FB. Enalapril and Enalaprilat Pharmacokinetics in Children with Heart Failure Due to Dilated

Cardiomyopathy and Congestive Heart Failure after Administration of an Orodispersible Enalapril Minitablet (LENA-Studies).Pharmaceutics. 2022 May 30;14(6):1163

3. Sinning C, Zengin E, Diller GP, Onorati F, Castel MA, Petit T, Chen YS, Lo Rito M, Chiarello C, Guillemain R, Coniat KN, Magnussen C, Knappe D, Becher PM, Schrage B, Smits JM, Metzner A, Knosalla C, Schoenrath F, Miera O, Cho MY, Bernhardt A, Weimann J, Goßling A, Terzi A, Amodeo A, Alfieri S, Angeli E, Ragni L, Napoleone CP, Gerosa G, Pradegan N, Rodrigus I, Dumfarth J, de Pauw M, François K, Van Caenegem O, Ancion A, Van Cleemput J, Miličić D, Moza A, Schenker P, Thul J, Steinmetz M, Warnecke G, Ius F, Freyt S, Avsar M, Sandhaus T, Haneya A, Eifert S, Saeed D, Borger M, Welp H, **Ablonczy L**, Schmack B, Ruhparwar A, Naito S, Hua X, Fluschnik N, Nies M, Keil L, Senftinger J, Ismaili D, Kany S, Csengeri D, Cardillo M, Oliveti A, Faggian G, Dorent R, Jasseron C, Blanco AP, Márquez JMS, López-Vilella R, García-Álvarez A, López MLP, Rocafort AG, Fernández ÓG, Prieto-Arevalo R, Zatarain-Nicolás E, Blanchart K, Boignard A, Battistella P, Guendouz S, Houyel L, Para M, Flecher E, Gay A, Épailly É, Dambrin C, Lam K, Ka-Lai CH, Cho YH, Choi JO, Kim JJ, Coats L, Crossland DS, Mumford L, Hakmi S, Sivathasan C, Fabritz L, Schubert S, Gummert J, Hübler M, Jacksch P, Zuckermann A, Laufer G, Baumgartner H, Giamberti A, Reichenspurner H, Kirchhof P. Study design and rationale of the pAtients pResenTing with cOngenital heaRt dIseAse Register (ARTORIA-R).ESC Heart Fail. 2021 Dec;8(6):5542-5550.

4. The First 5 Years of the Newest Eurotransplant Member State: Hungarian Results of International Organ Exchange From 2014 to 2018. Mihály S, Smudla A, **Ablonczy L**, Kóbori L, Nemes B, Rényi-Vámos F, Szabolcs Z, Szakály P, Kalmár Nagy K, Szederkényi E, Auer B, Deme O, Egyed-Varga A, Holtzinger E, Vida-Mező A, Nacsa J, Szilvási A, Merkely B.Transplant Proc. 2021 Jun;53(5):1394-1401.
5. Constantin T, Andrási N, Ponyi A, Goschler Á, **Ablonczy L**, Kincs J, Csóka M, Egyed B, Horváth Z, Kalocsai K, Káposzta R, Kardics K, Kemény V, Mosdósi B, Pék T, Szabó Z, Tóth A, Tory K, Tölgyesi A, Ónozó B, Vágó H, Vilmányi C, Peter W, Szekanecz Z, Kovács G, Szabó A. Diagnosis and treatment of paediatric multisystem inflammatory syndrome]. Orv Hetil. 2021 Apr 10;162(17):652-667.
6. Burckhardt BB, Ciplea AM, Laven A, **Ablonczy L**, Klingmann I, Läer S, Kleine K, Dalinghaus M, Đukić M, Breur JMPJ, van der Meulen M, Swoboda V, Schwender H, Lagler FB. Simulation Training to Improve Informed Consent and Pharmacokinetic/Pharmacodynamic Sampling in Pediatric Trials. Front Pharmacol. 2020 Dec 11;11:603042
7. Becher PM, Schrage B, Weimann J, Smits J, Magnussen C, Reichenspurner H, Goßling A, Rodrigus I, Dumfarth J, de Pauw M, François K, van Caenegem O, Ancion A, Van Cleemput J, Milicic D, Moza A, Schenker P, Röhrich L, Schönrath F, Thul J, Steinmetz M, Schmack B, Ruhparwar A, Warnecke G, Rojas SV, Sandhaus T, Haneya A, Eifert S, Welp H, **Ablonczy L**, Wagner F, Westermann D, Bernhardt AM, Knappe D, Blankenberg S, Kirchhof P, Zengin E,

Sinning C. Clinical characteristics and outcomes of patients with adult congenital heart disease listed for heart and heart–lung transplantation in the Eurotransplant region J Heart Lung Transplant. 2020 Nov;39(11):1238-1249.

8. Czobor NR, Ocsovszky Z, Csabai M, Róth G, Konkolÿ Thege B, **Ablonczy L**, Székely E, Gál J, Székely A. Long-term psychological effects of pediatric cardiac surgery].Orv Hetil. 2020 Oct 18;161(42):1787-1796.
9. Review of the discard and/or refusal rate of offered donor hearts to pediatric waitlisted candidates. Schweiger M, Everitt MD, Chen S, Nandi D, Castro J, Gupta D, Scheel J, Lal AK, **Ablonczy L**, Kirk R, Miera O, Davies RR, Dipchand AI. Pediatr Transplant. 2020 May;24(3):e13674.
10. Kirk R, Dipchand AI, Davies RR, Miera O, Chapman G, Conway J, Denfield S, Gossett JG, Johnson J, McCulloch M, Schweiger M, Zimpfer D, **Ablonczy L**, Adachi I, Albert D, Alexander P, Amdani S, Amodeo A, Azeka E, Ballweg J, Beasley G, Böhmer J, Butler A, Camino M, Castro J, Chen S, Chrisant M, Christen U, Danziger-Isakov L, Das B, Everitt M, Feingold B, Fenton M, Garcia-Guereta L, Godown J, Gupta D, Irving C, Joong A, Kemna M, Khulbey SK, Kindel S, Knecht K, Lal AK, Lin K, Lord K, Möller T, Nandi D, Niesse O, Peng DM, Pérez-Blanco A, Punnoose A, Reinhardt Z, Rosenthal D, Scales A, Scheel J, Shih R, Smith J, Smits J, Thul J, Weintraub R, Zangwill S, Zuckerman WA. ISHLT consensus statement on donor organ acceptability and management in pediatric

heart transplantation. J Heart Lung Transplant. 2020 Apr;39(4):331-341

11. The effects of parenteral prostacyclin therapy as add-on treatment to oral compounds in Eisenmenger syndrome.D'Alto M, Constantine A, Balint OH, Romeo E, Argiento P, **Ablonczy L**, Skoro-Sajer N, Giannakoulas G, Dimopoulos K.Eur Respir J. 2019 Nov 21;54(5):1901401.
12. Bajcetic M, de Wildt SN, Dalinghaus M, Breitkreutz J, Klingmann I, Lagler FB, Keatley-Clarke A, Breur JM, Male C, Jovanovic I, Szatmári A, **Ablonczy L**, Burckhardt BB, Cawello W, Kleine K, Obarcanin E, Spatenkova L, Swoboda V, van der Meulen M, Wagner P, Walsh J, Läer S. Orodispersible minitablets of enalapril for use in children with heart failure (LENA): Rationale and protocol for a multicentre pharmacokinetic bridging study and follow-up safety study.Contemp Clin Trials Commun. 2019 Jun 8;15:100393
13. Nemes B, Szederkényi E, Nagy KK, Hartyánszky I, **Ablonczy L**, Vámos FR, Mihály S, Máthé Z. A Summary of Transplantation Activity in Hungary. Transplant Proc. 2019 May;51(4):1202-1208.
14. Castro Díez C, Khalil F, Schwender H, Dalinghaus M, Jovanovic I, Makowski N, Male C, Bajcetic M, van der Meulen M, de Wildt SN, **Ablonczy L**, Szatmári A, Klingmann I, Walsh J, Läer S. Pharmacotherapeutic management of paediatric heart failure and ACE-I use patterns: a European survey. BMJ Paediatr Open. 2019 Jan 31;3(1):e000365

15. Kis E, **Ablonczy L**, Reusz GS Cardiac Magnetic Resonance Imaging of the Myocardium in Chronic Kidney Disease. Kidney Blood Press Res. 2018;43(1):134-142.
16. Czobor NR, Roth G, Prodán Z, Lex DJ, Sápi E, **Ablonczy L**, Gergely M, Székely EA, Gál J, Székely A. Chylothorax after pediatric cardiac surgery complicates short-term but not long-term outcomes-a propensity matched analysis. J Thorac Dis. 2017 Aug;9(8):2466-2475.
17. Gergely M, **Ablonczy L**, Székely EA, Sápi E, Gál J, Szatmári A, Székely A. Assessment of global tissue perfusion and oxygenation in neonates and infants after open-heart surgery.Interact Cardiovasc Thorac Surg. 2014 Apr;18(4):426-31.
18. Hartyánszky I, Kollár A, Kádár K, **Ablonczy L**, Novák E, Tóth A. Role of the Ross-procedure in the management of congenital heart defects.Orv Hetil. 2013 Feb 10;154(6):219-24.
19. Vertesaljai M, Piroth Z, Fontos G, Andreka G, Font G, Szantho G, Lueff S, Reti M, Masszi T, **Ablonczy L**, Juhasz ED, Simor T, Turner MS, Andreka P. Drugs, gene transfer, signaling factors: a bench to bedside approach to myocardial stem cell therapy.Heart Fail Rev. 2008 Jun;13(2):227-44.