RESEARCH LETTER

Epoprostenol therapy for pulmonary arterial hypertension: the first Polish experience

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Received: November 5, 2018.
Revision accepted: December 11, 2018.
Published online: December 13, 2018.
Conflict of interest: GK and PP report personal fees from AOP Orphan, MSD, Bayer, and Actelion. MW, KJ, JS, and WM report personal fees from AOP Orphan, MSD, and Actelion.
Pol Arch Intern Med. 2019; 129 (1): 65-68
doi:10.20452/pamw.4390

Introduction Epoprostenol is the only treatment shown to reduce mortality in patients with idiopathic pulmonary arterial hypertension (IPAH) in a randomized controlled study.[1] Due to a short half-life, it requires continuous administration by means of an infusion pump through a permanent tunneled catheter. Japanese studies showed that epoprostenol treatment in patients with pulmonary arterial hypertension (PAH) was associated with excellent prognosis never reported in the Caucasian population. In a study by the Matsubara group,[2] the 10-year survival rate was 78%. This was attributed to a significant hemodynamic improvement resulting from an early initiation and fast escalation of epoprostenol dose. When mean pulmonary arterial pressure (mPAP) was lowered to less than 42.5 mm Hg, the 10-year survival rate approached 100%, as compared with 50% when mPAP remained higher than 42.5 mm Hg despite treatment.[2] Doses of epoprostenol used in these studies[3] were much higher than typical doses used in the European centers.[4] Consequently, the reduction of mPAP reached 30% in the Japanese population[5] and only approximately 10% in the European studies.[6]

Epoprostenol therapy has been available for Polish patients with PAH since July 2015. In this single-center case series, we present the first Polish experience with this therapy.

Methods **Patients** In this retrospective case series analysis, we included consecutive adult patients with PAH from a single pulmonary hypertension reference center, treated with intravenous epoprostenol (Veletri; Actelion Pharmaceuticals, Allschwil, Switzerland) for at least 1 year. The eligible patients had IPAH or PAH associated with connective tissue disease and an mPAP of 50 mm Hg or higher at therapy initiation. According to the standards of the National Health Fund, only patients who were in World Health Organization (WHO) functional class IV or patients with WHO functional class III and ineffective previous medical therapy were enrolled. The therapy was considered ineffective when at least one of the following parameters was abnormal: cardiac index of less than 2.5 ml/min/m^2, right atrial pressure of 8 mm Hg or higher, and pulmonary artery blood saturation of 65% or lower.

The institutional ethics committee approved the study protocol, and informed consent was obtained from all patients for the use of their anonymous data in the present publication. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Clinical assessment Patients were routinely assessed before initiation of epoprostenol and after at least 12 months of treatment. Clinical assessment included demographic data, WHO functional class, measurement of N-terminal fragment of the prohormone brain natriuretic peptide (NT-proBNP), and distance in 6-minute walk test.[7] Hemodynamic evaluation was performed during right heart catheterization using a Swan-Ganz catheter.[8] Cardiac output was assessed using the oxygen consumption method.

Pulmonary arterial hypertension severity grade Patients' risk was estimated based on the Swedish PAH Register grading system.[9] Variables included in the risk assessment table from the guidelines of the European Society of Cardiology[10] were assigned 1, 2, or 3 points according to the cut-off values for low, intermediate, and high risk. Dividing the sum of all grades by the number of assessed variables for each patient rendered a mean PAH severity grade, which was rounded off to the nearest integer to classify patients to specific risk groups.

Quality of life assessment Quality of life was assessed with the 36-item Short Form questionnaire (license number QM044 886) before initiation of

TABLE 1 Clinical and hemodynamic characteristics of patients at baseline and at 12 months of epoprostenol treatment

Parameter		Baseline	1-year follow-up	Median change at 1-year follow-up
WHO-FC, n (%)	II	0 (0)	5 (50)	5
	III	3 (30)	5 (50)	2
	IV	7 (70)	0 (0)	–7[a]
NT-proBNP, pg/ml		2202.5 (1128–3376)	278 (110–579)	–988.5 (–3177 to –619)[a]
6MWD, m		322 (300–420)	409 (360–429)	74 (9–132)[a]
Right atrial area, cm^2		26.7 (23.0–31.0)	22.5 (19–29)	–3 (–7 to 1)
Hemodynamic parameters				
mRAP, mm Hg		5.5 (2–8)	2.5 (1–5)	0 (–6 to 1)
mPAP, mm Hg		52.5 (51–63)	42.5 (38–45)	–10.5 (–23 to –7)[b]
CI, $l/min/m^2$		2.2 (1.7–2.5)	2.8 (2.5–3.3)	0.64 (0.19–1.45)[b]
PVR, WU		12.4 (8.9–14.7)	7.8 (6.3–10.4)	–5.5 (–10 to –2.5)[b]
Quality of life				
Physical functioning		30 (15–45)	62.5 (45–80)	30 (10–50)[a]
Role-physical		21.9 (6.3–31.3)	56.3 (25–56.3)	21.9 (6.3–50)
Bodily pain		79 (52–100)	57 (41–100)	–11 (–43 to 48)
General health		37.5 (30–50)	52 (30–57)	7 (0–12)[a]
Vitality		43.8 (25–50)	59.4 (43.8–75)	21.9 (6.3–31.3)[a]
Social functioning		56.3 (50–75)	81.3 (62.5–100)	12.5 (0–37.5)
Role-emotional		62.5 (50–91.7)	75 (58.3–91.7)	4.2 (0–50)
Mental health		67.5 (55–75)	70 (55–80)	10 (0–15)
Physical component summary		40 (30.3–38.6)	41 (34.9–45.6)	5.3 (–2.7 to 15.3)
Mental component summary		41 (38–53)	50.6 (43.7–54.3)	3.3 (–0.2 to 9)

Data are presented as median (interquartile range).

a $P < 0.05$; **b** $P < 0.01$

The physical component summary was calculated based on the results of physical functioning, role-physical, bodily pain, and general health scores and the mental component summary based on vitality, social functioning, role--emotional, and mental health scores.

Abbreviations: 6MWD, 6-minute walking distance; CI, cardiac index; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; NT-proBNP, N-terminal fragment of the prohormone brain natriuretic peptide; PVR, pulmonary vascular resistance; WHO-FC, World Health Organization functional class

epoprostenol therapy and at follow-up. The data were analyzed using Certified Scoring Software 5.0TM (OPTUM, Eden Praire, Minnesota, United States). The quality of life was evaluated in 8 domains listed in TABLE 1.

Epoprostenol therapy Epoprostenol was infused by the central indwelling catheter as previously described.[11] The target dose at hospital discharge was approximately 20 ng/kg/min. It was further increased at home or at additional hospitalization. The decision on the dose increase was based on patient's tolerance and clinical response.

Hemodynamic response to epoprostenol therapy Hemodynamic response was defined as a decrease of mPAP to less than 42.5 mm Hg at follow-up catheterization. We considered the following variables as potential predictors of hemodynamic response: age, maximal dose of epoprostenol, time from diagnosis of PAH to initiation of epoprostenol, use of additional PAH-specific therapies, and initiation of epoprostenol therapy as a first- or second-line therapy.

Statistical analysis Continuous variables were reported as median and interquartile range (IQR) and categorical variables as counts and percentages. For the comparison of different variables at baseline and at follow-up, we used the Wilcoxon and McNemar tests as appropriate. To find predictors of hemodynamic response, we compared several parameters (age, sex, maximal dose of epoprostenol, the use of additional PAH--targeted therapies, time from diagnosis to initiation of epoprostenol therapy, and markers of disease severity such as the level of NT-proBNP, mPAP, mean right atrial pressure, pulmonary vascular resistance, and cardiac index) between patients with and without hemodynamic response to epoprostenol, using the Mann–Whitney test and the χ^2 test with Yates correction for the continuous and categorical variables, respectively. The significance level was set at an α level of

0.05. The values were presented as median (interquartile range). Statistical analysis was performed with the use of Dell Inc. (2016), Dell Statistica (data analysis software system), version 13 (software.dell.com).

Results

Study population Between July 2015 and January 2018, we initiated epoprostenol therapy in 18 patients with PAH. Of the study group, 4 patients died: 1 of ovarian cancer and 3 of PAH progression. Two patients with IPAH were admitted to our hospital with an end-stage disease with severe hemodynamic compromise requiring inotropic support. The rescue treatment with epoprostenol was unsuccessful, and these patients died during the same hospitalization at which epoprostenol was started. One patient with PAH associated with connective tissue disease was treated with epoprostenol for 9 months and died shortly after pericardiocenthesis performed due to a large amount of pericardial fluid. For the purpose of the present analysis, we included the first 10 patients (median age, 47.5 years [IQR, 41–62 years]; 9 women), who completed the 1-year follow-up. The clinical characteristics of the patients are presented in TABLE 1. The median time between the diagnosis of PAH and the initiation of epoprostenol treatment was 8 (IQR, 0–33) months. At enrollment, 3 patients were treatment naive, 3 patients were receiving phosphodiesterase-5 inhibitor (PDE5i) and endothelin receptor antagonist, 3 were receiving PDE5i in monotherapy, and 1 was receiving PDE5i combined with oral treprostinil. At 1-year follow-up, patients were treated with sildenafil and epoprostenol (n = 7), sildenafil, epoprostenol, and bosentan (n = 2), or epoprostenol monotherapy (n = 1). At the time of the study, a triple combination therapy was not reimbursed in Poland. The median dose of epoprostenol at 1-year follow-up was 32.7 (IQR, 24.9–62.5) ng/kg/min and ranged from 19.6 to 74.6 ng/kg/min. The median risk severity grade was 2.4 (IQR, 2.3–2.6); 6 patients were in the intermediate-risk group and 4 were in the high-risk group.

Clinical and hemodynamic effects of epoprostenol therapy At 1-year follow-up, we observed improvement in the WHO functional class in 7 patients and no change in 3 patients. Changes in other clinical parameters are shown in TABLE 1.

The median severity risk grade decreased from 2.4 (IQR, 2.3–2.6) to 1.7 (IQR, 1.7–1.9) (P = 0.005). The risk status changed from high to intermediate in 3 patients, from high to low in 1 patient, and from intermediate to low in 1 patient; 5 patients remained in the intermediate risk group.

Quality of life We observed an improvement in physical functioning, physical role, general health, and vitality domains of the 36-item Short Form questionnaire scale at 1-year follow-up, as shown in TABLE 1.

Side effects The patients reported side effects typical for epoprostenol therapy. As previously reported, we also observed 7 episodes of an indwelling central catheter occlusion in 4 patients.[11] Additionally, 1 episode of catheter leak was reported, and it was repaired with the dedicated kit.

Potential predictors of hemodynamic improvement after treatment Five patients achieved an mPAP of less than 42.5 mm Hg. As compared with those in whom mPAP remained higher than 42.5 mm Hg at follow-up, they were characterized by a shorter median time from the diagnosis of PAH to initiation of epoprostenol therapy (0 [IQR, 0–4] months vs 32 [IQR, 26–40] months, P = 0.04) and a higher proportion of patients in whom epoprostenol was initiated as a first-line therapy (4 [80%] vs 0 of patients, P = 0.05). We did not find differences between these 2 groups in the other analyzed parameters.

Discussion

Our study shows for the first time that in Polish patients with PAH epoprostenol therapy significantly improves their quality of life, physical capacity, and hemodynamic profile. We observed a median decrease of mPAP of 10 mm Hg, which is much higher than that observed in clinical studies with other PAH therapies. Importantly, despite significant side effects typical of prostacyclin therapies and the need for continuous infusion, epoprostenol increased the quality of life of treated patients in both mental and physical domains.

The best hemodynamic effect of epoprostenol therapy was achieved when used early in the disease course. In contrast to previous reports, we were not able to show the relationship between the dose of epoprostenol and the magnitude of mPAP decrease. This may have resulted from a small number of enrolled patients and the influence of potential confounding factors, including severity and duration of the disease, individual patients' characteristics, and others.

The challenges associated with the initiation of epoprostenol therapy were previously described for Polish specialists in pulmonary hypertension.[12]

Conclusions

Epoprostenol use in patients with severe PAH decreased their risk status and significantly improved their physical capacity, hemodynamic profile, and quality of life. Early initiation of therapy with epoprostenol and its use as the first-line therapy characterized patients with the most significant hemodynamic response. Further studies are needed to identify the predictors of favorable response to epoprostenol in the Caucasian population with PAH.

ACKNOWLEDGMENTS The study was supported by the Actelion research grant, grant No: 1177/2017/DW, recipient: John Paul II Hospital in Kraków.

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