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The Journal of Heart and Lung Transplantation

http://www.jhltonline.org

Intravenous treprostinil as an add-on therapy in patients with pulmonary arterial hypertension

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KEYWORDS:
pulmonary hypertension;
pulmonary arterial hypertension;
treprostinil;
prostacyclin;
risk assessment;
mortality

BACKGROUND: In patients with pulmonary arterial hypertension who have an insufficient response to oral or inhaled therapies, current guidelines recommend the use of parenteral prostacyclin analogues, although the efficacy of this approach is unknown.

METHODS: This retrospective multicenter study evaluated patients with pulmonary arterial hypertension who received intravenous treprostinil as an add-on therapy. The risk at baseline and follow-up (6−12 months after the initiation of treprostinil) was classified as low, intermediate, or high according to current recommendations. The outcome was measured as transplant-free survival after the initiation of treprostinil therapy.

RESULTS: A total of 126 patients were analyzed, almost all of them pre-treated with combinations of other pulmonary arterial hypertension medications. Before the initiation of intravenous treprostinil, 2 (2%) patients had a low-risk profile; 100 (79%), an intermediate-risk profile; and 24 (19%), a high-risk profile. At follow-up, 24 (19%) patients were classified as low-risk. These patients had a 5-year transplant-free survival rate >90%. In contrast, patients who remained at intermediate or high risk had transplant-free survival rates of 76%, 43%, and 28% at 1, 3, and 5 years, respectively. Failure to reach a low risk at follow-up was an independent predictor of transplant-free survival (hazard ratio, 9.25; 95% confidence interval, 1.20−71.60; $p = 0.033$ 1).

CONCLUSIONS: Risk assessment at 6−12 months after the initiation of add-on intravenous treprostinil in patients with an insufficient response to nonparenteral treatments allows the prediction of transplant-free survival over the ensuing years. Achieving a low-risk profile is associated with excellent outcomes, whereas mortality is high in patients who remain at intermediate or high risk.

J Heart Lung Transplant 2019;38:748−756

Pulmonary arterial hypertension (PAH) is a rare disease characterized by pulmonary vascular remodeling that often progresses rapidly, leading to right-sided heart failure and death if not effectively treated. The angio-obliterative nature of the disease was largely characterized between the 1960s and 1970s,[1,2] but it took several decades of research until active treatments became available. In 1995, the US

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1053-2498/$ - see front matter
https://doi.org/10.1016/j.healun.2019.05.002

Food and Drug Administration approved intravenous epoprostenol, a prostacyclin analogue, as the first drug for the treatment of PAH.[3] For several years, intravenous epoprostenol remained the only medical treatment option for these patients (except for a small subgroup with a vasoreactive phenotype who respond to calcium channel blockers).

Since the turn of the century, treatment options for PAH have increased with the introduction of oral drugs (e.g., endothelin receptor antagonists, phosphodiesterase-5 [PDE5] inhibitors, stimulators of the soluble guanylate cyclase, and prostacyclin receptor agonists).[4,5] In addition, further prostacyclin derivatives have been developed, including treprostinil, a substance with a longer plasma half-life than epoprostenol,[6] which is available for intravenous, subcutaneous, oral, and inhaled application. Today, intravenous prostacyclin analogues are used predominantly as rescue therapy in patients with very severe disease and in patients with an insufficient response to oral or inhaled drugs.

Given that more than 10 PAH drugs are now approved and available in many countries, treatment decisions have become increasingly complex. Current guidelines recommend an individualized risk-based approach.[4,5,7] Risk is determined by a set of clinical, laboratory, and hemodynamic variables that can be used at any time point during the course of the disease to estimate the likelihood of death (or the need for lung transplantation) over the ensuing years. The principle goal of PAH treatment is to reach a low-risk profile, which is usually accompanied by 5-year survival rates of 90% or higher.[8–11] Patients not reaching a low-risk profile have an insufficient response to therapy and require additional treatments.[4,5,7]

The majority of patients with newly diagnosed PAH present with a low- or intermediate-risk profile, and most of these patients receive oral therapies, predominantly endothelin receptor antagonists and PDE5 inhibitors, either alone or in combination.[8,12] The individual response to treatment is highly variable, and follow-up evaluations are required to determine whether or not a low-risk profile has been achieved. According to various PAH registries, the majority of patients do not reach a low-risk profile with endothelin receptor antagonists/PDE5 inhibitor-based treatments.[8,10,12] For these patients, treatment options remain limited. Oral or inhaled treprostinil as additional therapies did not affect the outcomes in short-term trials.[13–17]

Given the high mortality risk of patients with an insufficient response to their initial medication, current guidelines recommend that physicians consider the use of intravenous prostacyclin analogues as an add-on therapy in such cases.[4,5,7] Although intravenous prostacyclin analogues are often considered particularly effective in PAH, most of the available data for these compounds date back to the time when other PAH drugs were not available. There is very little evidence on the efficacy of intravenous prostacyclin analogues in patients who have an insufficient response to other PAH therapies. Randomized controlled trials and outcome studies in this setting have not been performed.

In this study, we analyzed the clinical courses of 126 PAH patients who had received intravenous treprostinil because of an insufficient response to other PAH therapies. The main objectives were the following: (1) to describe the long-term outcomes of these patients, (2) to identify predictors of a favorable response (defined as achieving a low-risk profile at follow-up), and (3) to identify predictors of a poor outcome (i.e., death or the need for lung transplantation).

Methods

This was a retrospective study including all patients with PAH who had received intravenous treprostinil initiated as add-on therapy to other PAH drugs between December 2009 and June 2018 at the three participating centers (Hannover Medical School, University of Giessen, and University of Greifswald, all in Germany). These centers entered the data of their patient prospectively into their hospital data bases.[18] The follow-up ended on September 1, 2018. All patients gave written informed consent for the use of their anonymized data for scientific purposes. According to German law, Institutional Review Board approval is not required for retrospective data collection; however, the local Institutional Review Board were informed about the nature of this data collection in conjunction with the approval of the respective local registries.

Patients and assessments

Patients were selected for this study based on the following criteria: (1) a diagnosis of PAH according to current criteria, (2) age ≥18 years, and (3) the start of intravenous treprostinil at least 3 months after the initiation of PAH therapy. Excluded from this analysis were children, patients with other forms of pulmonary hypertension, and patients who received intravenous treprostinil as part of the initial treatment of newly diagnosed PAH (upfront combination therapy).

This starting point of the study was the date when intravenous treprostinil treatment was initiated. Baseline assessments, obtained prior to the start of intravenous treprostinil, included hemodynamics from right heart catheterization, 6MWD, FC, and serum levels of brain natriuretic peptide (BNP) or the N-terminal fragment of probrain natriuretic peptide (NT-proBNP). Follow-up assessments were based on the same variables obtain between month 6 and month 12 after initiation of intravenous therapy.

Risk assessment was based on right atrial pressure, cardiac index, mixed-venous oxygen saturation (SvO_2), FC, 6MWD, and BNP/NT-proBNP as described previously (Table 1).[10,12] Based on the cut-off levels proposed in the current ESC/ERS guidelines, each variable was graded as "1" (low risk), "2" (intermediate risk), or "3" (high risk), and the average risk was calculated by dividing the sum of the grades by the number of variables and rounding to the next integer.

In the participating centers, the need for intravenous treprostinil treatment routinely triggered an evaluation for lung transplantation. Eligible patients were actively listed once all other treatment options had been exhausted.

Intravenous treprostinil treatment

The decision to initiate intravenous treprostinil therapy did not follow a pre-specified protocol but was left to the discretion of the physicians in charge and their patients. All the patients were hospitalized for the initiation of intravenous treprostinil. Treatment was started at a dose of 1.25 ng/kg/min and was gradually increased to the maximum tolerated dose. Afterward, treprostinil

Table 1 Variables and Cut-Off Values Used for Risk Assessment

Variable	Low risk	Intermediate risk	High risk
WHO FC	I/II	III	IV
6-min walk distance	>440 m	165–440 m	<165 m
BNP	<50 ng/liter	50–300 ng/liter	>300 ng/liter
NT-proBNP	<300 ng/liter	300–1,400 ng/liter	>1,400 ng/liter
RA pressure	<8 mm Hg	8–14 mm Hg	>14 mm Hg
Cardiac index	≥2.5 liter/min/m^2	2.0–2.4 liter/min/m^2	<2.0 liter/min/m^2
SvO_2	>65%	60%–65%	<60%

BNP, brain natriuretic peptide; NT-proBNP, N-terminal fragment of probrain natriuretic peptide; RA, right atrial; SvO_2, mixed-venous oxygen saturation; WHO FC, World Health Organization Functional Class.

was administered via a fully implantable pump (Lenus Pro, Tricumed Medizintechnik GmbH, Kiel, Germany) with further individual dose adjustments targeting the highest tolerated dose.[19,20]

Statistical analysis

We used IBM SPSS Statistics 25.0 (IBM Corp, Armonk, NY, USA) and Stata 13.0 (State Corp LP, College Station, Texas, USA) statistical software to analyze the data. Continuous variables are shown as median and interquartile range. Categorical variables are shown as numbers and percent (%). For comparisons of patient populations, Fisher's exact test, Chi-square test, Mann-Whitney-U test, or two-sided t-tests were used as appropriate.

The risk was assessed at baseline and at follow-up as described above. The outcome was measured as transplant-free survival. Kaplan–Meier estimates on transplant-free survival were made for the whole group and according to the risk status at baseline and follow-up. Patients who died before the first follow-up were assigned a high-risk status before death. Additional Kaplan–Meier survival estimates were made for the subgroups of patients with idiopathic or heritable PAH as well as for patients with a scleroderma phenotype, which consisted of patients with systemic sclerosis and mixed connective tissue disease, and for patients with congenital heart disease-associated PAH. The starting point for all survival analyses was the date when intravenous treprostinil was initiated. Survivors were censored at the end of the follow-up period. Between-group comparisons were made by log-rank analyses.

Variables associated with a favorable response to intravenous treprostinil were determined by logistic regression analysis using group medians for continuous variables. Simple Cox regression analysis was performed to identify the predictors of a poor outcome, which was defined as lung transplantation or death. For multivariate analyses, variables with a p-value < 0.1 were tested in a stepwise forward Cox regression model. For all regression analyses, continuous variables were dichotomized by the respective group medians.

Results

A total of 126 patients (30 from Giessen, 53 from Greifswald and 43 from Hannover) were enrolled in this study. The characteristics of the patients at baseline (i.e., prior to initiation of intravenous treprostinil) are shown in Table 2. The majority of the patients ($n = 100$, 79%) presented with an intermediate-risk profile at that time; 2 (2%) had a low-risk profile and 24 (19%) a high-risk profile. All the patients were pre-treated with other PAH medications, almost all of them (98%) with combination therapies.

Risk assessment at follow-up

The interval between the initiation of intravenous treprostinil and the first comprehensive follow-up assessment was 10 (6–12) months. The dose of treprostinil at follow-up was 35 (24–45) ng/kg/min (41 [31–53] ng/kg/min in patients who reached a low-risk profile at follow-up, and 34 (24–44) ng/kg/min in patients who did not; $p = 0.362$).

Improvements from baseline to follow-up were seen for WHO FC, mean pulmonary artery pressure (PAPm), cardiac index, and pulmonary vascular resistance (PVR). The number of patients with FC I/II symptoms increased from 6% to 24% ($p = 0.0094$); PAPm decreased from 55 (48–64) mm Hg to 51 (45–58) mm Hg ($p = 0.005\ 9$), cardiac index increased from 2.2 (1.7–2.7) liter/min/m^2 to 2.6 (2.2–3.0) liter/min/m^2 ($p = 0.0039$), and PVR declined from 935 (687–1413) dyn·s·cm^{-5} to 695 (525–930) dyn·s·cm^{-5} ($p < 0.001$); the full data are provided in Supplementary Table S1 online. An improvement in the risk category from baseline to follow-up was noted in 33 (26%) patients; the risk category remained unchanged in 78 (60%) patients and deteriorated in 15 (12%) patients. Only 24 (19%) patients achieved a low-risk status at follow-up.

In the univariate analyses, baseline variables associated with a higher likelihood of achieving a low-risk status were age <48 years, WHO FC I or II, 6 min walking distance ≥331 m, and diffusion capacity of the lung for carbon monoxide (DLCO) ≥53% of the predicted value. In the multivariate model, only 6 min walking distance ≥331 m and DLCO ≥53% of the predicted value were independently associated with a higher likelihood of reaching a low-risk status (Table 3). A full list of variables included in the univariate and multivariate analyses is provided in Supplementary Table S2 online.

Transplant-free survival

During the observation period of 35 (17–56) months, 15 (12%) patients underwent lung transplantation and 40 (32%) died. For the entire group, the estimated transplant-free survival rates at 1, 3, and 5 years after the initiation of

Table 2 Characteristics of the Patients at Baseline

Variable	All patients	Patients who reached a low-risk status with IV treprostinil	Patients who did not reach a low-risk status with IV treprostinil	*p*-value (reaching a low-risk status vs not reaching a low-risk status)
	n = 126	*n* = 24	*n* = 102	
Age (years)	48 (36–63)	39 (31–57)	51 (39–63)	0.012
Female sex (%)	93 (74)	19 (79)	74 (73)	0.507
BMI (kg/m^2)	24 (22–28)	24 (22–26)	24 (21–28)	0.694
Diagnosis				
I/H/PAH, *n* (%)	91 (72)	19 (79)	72 (71)	0.423
PAH-SSc/MCTD, *n* (%)	16 (13)	1 (4)	15 (15)	0.163
PAH-CHD	13 (10)	2 (8)	11 (11)	0.722
Others[a]	6 (5)	2 (8)	4 (4)	0.361
Time since PAH diagnosis (months)	86 (54–137)	99 (62–135)	82 (52–137)	0.698
WHO FC				
I/II, *n* (%)	8 (6)	5 (21)	3 (3)	0.001
III, *n* (%)	97 (77)	16 (67)	81 (79)	0.182
IV, *n* (%)	21 (17)	3 (13)	18 (18)	0.543
6MWD (m)	331 (220–434)	438 (372–504)	297 (206–392)	0.002
BNP (ng/liter), *N* = 29	407 (195–719)	277 (63–407)	460 (212–757)	0.343
NT-proBNP (ng/liter), *N* = 62	2468 (1289–4459)	947 (594–2980)	3057 (1476–4875)	0.038
DLCO (% pred)	53 (34–64)	62 (57–77)	49 (33–63)	0.012
Hemodynamics				
RAP (mm Hg)	8 (6–12)	8 (7–11)	9 (6–13)	0.316
PAPm (mm Hg)	55 (48–64)	57 (44–64)	55 (48–64)	0.508
PAWP (mm Hg)	10 (8–13)	9 (6–12)	10 (8–13)	0.527
CI (liter/min/m^2)	2.2 (1.7–2.7)	2.4 (2.0–2.7)	2.1 (1.7–2.7)	0.244
PVR (dyn·s·cm^{-5})	935 (687–1413)	890 (715–1278)	977 (685–1428)	0.538
SvO_2 (%)	61 (55–66)	62 (57–67)	61 (55–66)	0.968
ESC/ERS risk status				
Low, *n* (%)	2 (2)	1 (4)	1 (1)	0.261
Intermediate, *n* (%)	100 (79)	20 (83)	80 (78)	0.593
High, *n* (%)	24 (19)	3 (13)	21 (21)	0.364
PAH medication before IV treatment				
ERA	124 (98)	23 (96)	101 (99)	0.879
PDE5i or sGCs	124 (98)	24 (100)	100 (98)	0.489
Inhaled PCA or oral PCRA	26 (21)	4 (17)	22 (22)	0.593
Monotherapy	2 (2)	1 (4)	1 (1)	0.626
Double combination therapy	98 (78)	19 (79)	79 (77)	0.451
Triple combination therapy	26 (21)	4 (17)	22 (22)	0.593

6MWD, 6-minute walking distance; BMI, body mass index; BNP, brain natriuretic peptide; CHD, congenital heart disease; CI, cardiac index; DLCO, diffusion capacity of the lung for carbon monoxide; ERA, endothelin receptor antagonists; ERS, European Respiratory Society; ESC, European Society of Cardiology; I/HPAH, idiopathic or heritable pulmonary arterial hypertension; IV, intravenous; MCTD, mixed connective tissue disease; NT-proBNP, N-terminal fragment of probrain natriuretic peptide; PAH, pulmonary arterial hypertension; PAPm, mean pulmonary arterial pressure; PAWP, pulmonary artery wedge pressure; PCA, prostacyclin analogues; PCRA, prostacyclin receptor agonists; PDE5i, phosphodiesterase-5 inhibitors; PVR, pulmonary vascular resistance; RAP, right atrial pressure; sGCs, stimulators of soluble guanylate cyclase; SSc, systemic sclerosis; SvO_2, mixed-venous oxygen saturation; WHO FC, World Health Organization Functional Class.

[a]Others include human immunodeficiency virus-associated pulmonary arterial hypertension (*n* = 1), portopulmonary PH (*n* = 2) and pulmonary arterial hypertension associated with systemic lupus erythematosus (*n* = 3)

intravenous treprostinil were 81%, 53%, and 42%, respectively (Figure 1). Among the patients who achieved a low-risk status at follow-up, the estimated transplant-free survival rates at 1, 3, and 5 years after the initiation of intravenous treprostinil were 100%, 94%, and 94%, respectively. In contrast, in patients who remained at intermediate or high risk, the estimated transplant-free survival rates at 1, 3, and 5 years were 76%, 43%, and 28%, respectively ($p < 0.001$ vs patients who achieved a low-risk status; Figure 2). The median transplant-free survival of the patients who did not achieve a low-risk profile after the initiation of treprostinil therapy was 2.1 years.

Patients with a high-risk profile at baseline tended to have lower estimated survival rates than the patients with an intermediate risk at baseline, although this difference was not statistically significant (Supplementary Figure S1 online). In contrast, the risk at follow-up was strongly associated with transplant-free survival. Patient with an intermediate risk at

Table 3 Baseline Variables Associated with Reaching a Low-Risk Profile 6–12 Months after the Initiation of Intravenous Treprostinil

	Univariate analysis		Multivariate analysis	
Variable	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
Age < median	2.96 (1.13–7.74)	0.027	—	—
WHO FC I/II	8.68 (1.91–39.44)	0.005	—	—
6MWD ≥ median	9.31 (2.56–33.95)	<0.001	5.24 (1.35–20.38)	0.017
DLCO ≥ median	5.45 (1.70–17.50)	0.004	4.54 (1.16–17.76)	0.030

6MWD, 6-minute walking distance; BMI, body mass index; BNP, brain natriuretic peptide; CHD, congenital heart disease; CI, cardiac index; DLCO, diffusion capacity of the lung for carbon monoxide; ERS, European Respiratory Society; ESC, European Society of Cardiology; I/HPAH, idiopathic or heritable pulmonary arterial hypertension; IV, intravenous; MCTD, mixed connective tissue disease; NT-proBNP, N-terminal fragment of probrain natriuretic peptide; PAPm, mean pulmonary arterial pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SSc, systemic sclerosis; SvO_2, mixed-venous oxygen saturation; WHO FC, World Health Organization Functional Class.

follow-up had transplant-free survival rates at 1, 3, and 5 years of 86%, 50%, and 33% whereas those with a high risk at follow-up had corresponding transplant-free survival rates of 45%, 21%, and 14% ($p < 0.0001$ for all group comparisons; Supplementary Figure S2 online).

In the univariate analyses, baseline predictors of mortality were cardiac index <2.2 liter/min/m^2 and PVR ≥ 935 dyn·s·cm^{-5}. At follow-up, the predictors of mortality were WHO FC III or IV, 6 min walk distance <346 m, BNP or NT-proBNP ≥ 380 ng/liter or 804 ng/liter, respectively, cardiac index <2.6 liter/min/m^2, SvO_2 < 64%, and failing to achieve a low-risk status. In the multivariate model, only failing to achieve a low-risk status was predictive of mortality (Table 4). A complete list of variables included in the univariate and multivariate analyses is provided in Supplementary Table S3 online.

Subgroup analyses

Subgroup analyses were performed for patients with idiopathic or heritable PAH (I/HPAH) ($n = 91$), for patients with SSc/MCTD-PAH ($n = 16$) and for patients with congenital heart disease (CHD)–PAH ($n = 13$). The baseline characteristics of these patients are shown in Supplementary Table S4 online. Only 1 (6%) patient with SSc/MCTD-PAH reached a low-risk profile with intravenous treprostinil, compared with 2 (15%) patients with CHD-PAH and 19 (21%) patients with I/HPAH.

The transplant-free survival of all three patient groups was similar. In patients with I/HPAH, the estimated transplant-free survival rates at 1, 3, and 5 years after the initiation of intravenous treprostinil were 77%, 50%, and 39%, respectively. In patients with SSc/MCTD-PAH and CHD-PAH, the

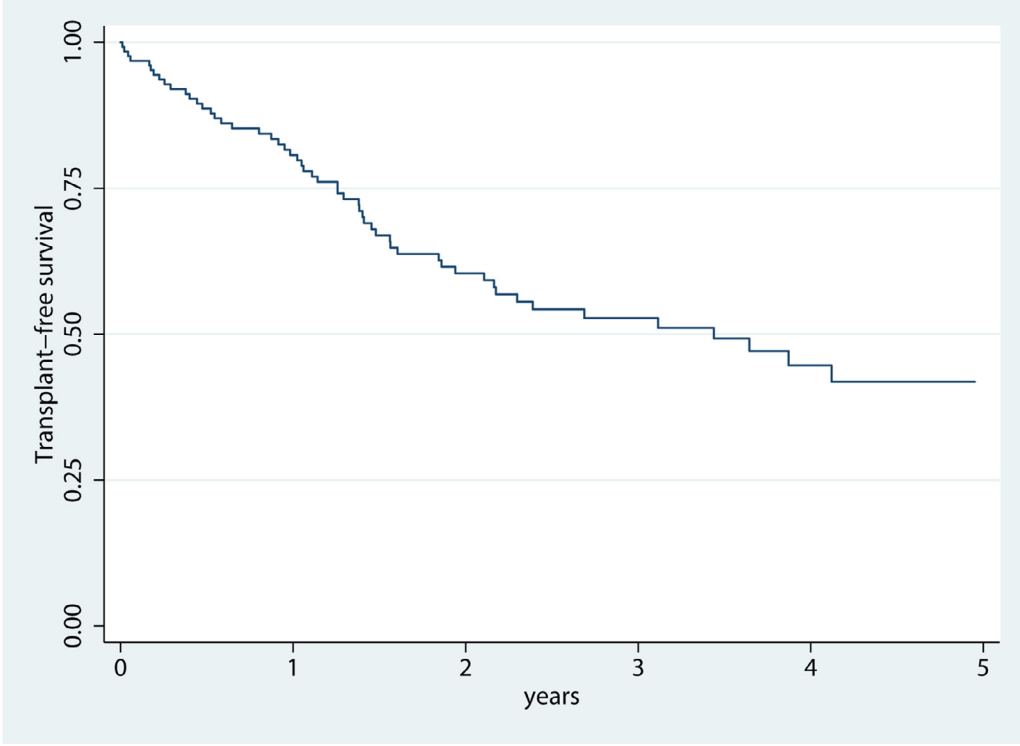

Figure 1 Kaplan–Meier estimates for transplantation-free survival from the start of intravenous treprostinil in the entire cohort Numbers at risk at baseline, 1 year, 2 years, 3 years, and 5 years were $n = 126$, $n = 88$, $n = 54$, $n = 33$, and $n = 6$, respectively.

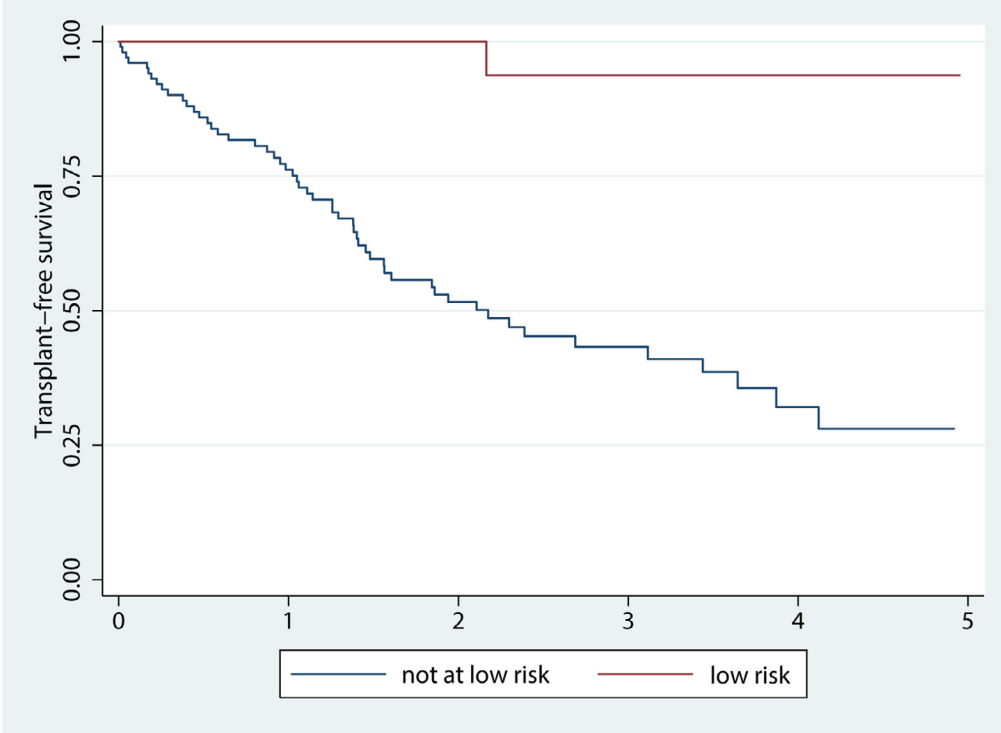

Figure 2 Kaplan–Meier estimates for transplantation-free survival in patients who achieved a low-risk status at follow-up and in patients who did not reach a low-risk status at follow-up

For the low-risk group, numbers at risk at baseline, 1 year, 2 years, 3 years and 5 years were $n = 24$, $n = 19$, $n = 17$, $n = 13$, and $n = 4$, respectively. For the not-at-low-risk group, numbers at risk at baseline, 1 year, 2 years, 3 years and 5 years were $n = 102$, $n = 69$, $n = 37$, $n = 20$, and $n = 2$, respectively.

corresponding survival rates were 81%, 62%, and 41%, and 100%, 49%, and 49%, respectively. None of the group comparisons were statistically significant (Figure 3).

Discussion

The main findings of the present study were as follows: (1) the overall survival rates at 1, 3, and 5 years after the initiation of intravenous treprostinil as an add-on treatment to other PAH therapies were 81%, 53%, and 42%, respectively; (2) only 33/126 (26%) patients improved their risk category from baseline to follow-up, and only 24/126 (19%) patients achieved a low-risk profile; (3) the long-term transplant-free survival rates were significantly higher in patients who reached a low-risk profile at follow-up than in patients who presented with an intermediate- or high-risk profile 6–12 months after the initiation of intravenous treprostinil; (4) the median survival of patients who did not achieve a low-risk profile after treprostinil initiation was 2.1 years; and (5) only one (6%) of 16 patients with SSc/MCTD-PAH reached a low-risk status with intravenous treprostinil.

These data are consistent with a recent publication by Bartolome and coworkers who studied the long-term effects of various parenteral prostacyclin analogues (intravenous epoprostenol, $n = 132$; intravenous treprostinil, $n = 25$; and

Table 4 Risk Factors for Adverse Outcomes, Death, or Lung Transplantation, after the Initiation of Intravenous Treprostinil

	Univariate analysis		Multivariate analysis	
Variable	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
WHO FC III/IV at follow-up	4.63 (1.83–11.71)	0.0012	—	—
6MWD at follow - up < median	3.53 (1.82–6.85)	0.0002	—	—
BNP/NT-proBNP at follow-up ≥ median	4.09 (1.92–8.70)	0.0003	—	—
CI at baseline < median	2.26 (1.28–4.00)	0.0049	—	—
PVR at baseline ≥median	2.16 (1.22–3.82)	0.0084	—	—
SvO_2 at follow-up < median	2.47 (1.01–6.00)	0.0466	—	—
Intermediate or high risk at follow-up	21.26 (2.92–154.86)	0.0026	9.25 (1.20–71.60)	0.0331
High risk at follow-up	4.35 (2.46–7.69)	<0.0001	—	—

6MWD, 6-minute walking distance; BNP, brain natriuretic peptide; CI, cardiac index; NT-proBNP, N-terminal fragment of probrain natriuretic peptide; PVR, pulmonary vascular resistance; SvO_2, mixed-venous oxygen saturation; WHO FC, World Health Organization Functional Class.

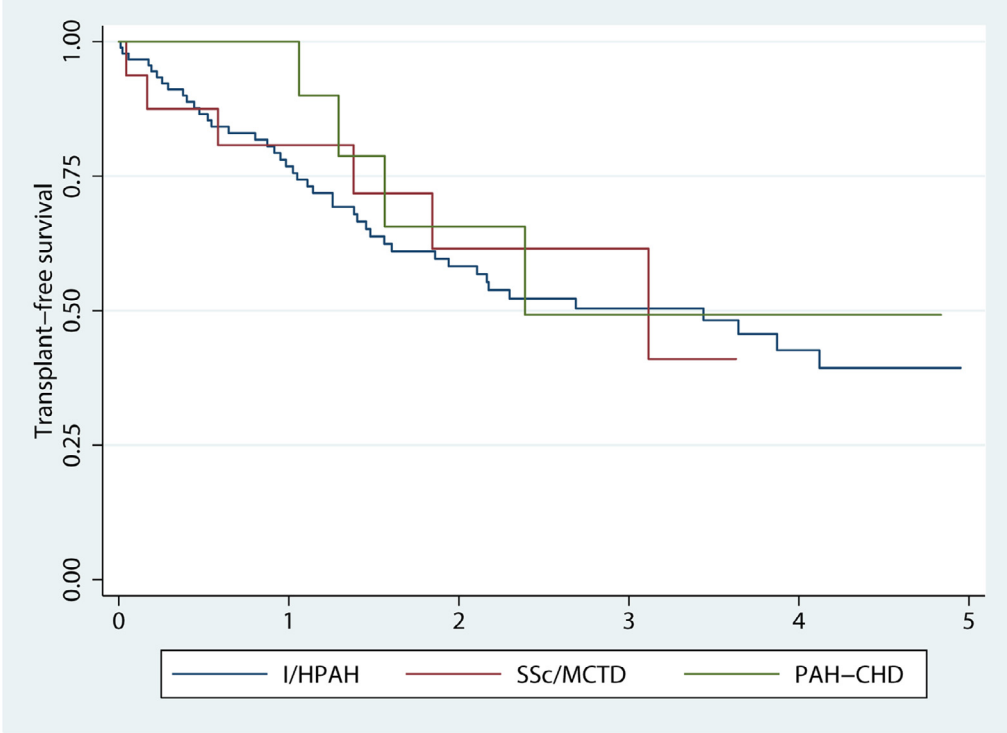

Figure 3 Kaplan–Meier estimates for transplantation-free survival from the start of intravenous treprostinil in patients with I/HPAH, patients with SSc/MCTD-PAH and patients with CHD-PAH

For the I/HPAH group, numbers at risk at baseline, 1 year, 2 years, 3 years, and 5 years were $n = 91$, $n = 62$, $n = 42$, $n = 26$, and $n = 5$, respectively. For the SSc/mixed connective tissue disease (MCTD) group, numbers at risk at baseline, 1 year, 2 years, 3 years, and 5 years were $n = 16$, $n = 11$, $n = 5$, $n = 3$, and numbers (n) = 0, respectively. For the CHD group, numbers at risk at baseline, 1 year, 2 years, 3 years, and 5 years were $n = 13$, $n = 10$, $n = 4$, $n = 2$, and $n = 0$, respectively.

subcutaneous treprostinil, $n = 38$) in patients with PAH, most of whom had been pre-treated with other PAH medications.[21] In that study, approximately 35% of the patients reached a low-risk status (as defined by reaching 2 or more out of 4 distinct low-risk criteria) after the initiation of parenteral prostacyclin analogues. These patients had a 3-year transplant-free survival rate of approximately 90%, which is comparable to our series. In the remaining 65% of the patients who did not reach a low-risk status at follow-up, the median transplant-free survival rate was approximately 2 years, which was, again, similar to our data.

Taken together, these data are sobering, and they help put into perspective the role of intravenous prostacyclin analogues as an add-on therapy for PAH patients who fail other treatment options. From our findings and the data of Bartolome and coworkers,[21] it is evident that patients who achieve a low-risk category at follow-up have an excellent survival over the ensuing years. The majority of patients, however, do not achieve a low-risk status, and the risk of death in these patients is very high. This information is of particular importance for patients in whom lung transplantation is considered. It is recommended that potentially eligible patients with PAH are evaluated for lung transplantation once they are in need of parenteral prostacyclin therapy.[9] In patients failing to reach a low-risk status within 6 −12 months of treatment with parenteral prostacyclin analogues, active listing for lung transplantation should be strongly considered.

Our findings reinforce the notion that the treatment strategies for PAH must aim at achieving a low-risk profile.[7] At the same time, our data show that it is almost impossible to predict the response to intravenous treprostinil. Patients with a 6 min walk distance ≥331 m and a DLCO ≥53% of the predicted value at baseline were more likely to achieve a low-risk status, but none of the investigated baseline variables allowed for a reliable identification of future responders. Our data suggest that patients with SSc/MCTD-PAH may be less likely than patients with idiopathic PAH to achieve a low-risk profile with add-on intravenous treprostinil therapy, but this observation requires confirmation by larger studies.

We can only speculate on the reasons why intravenous treprostinil failed to achieve a low-risk profile in the majority of our patients. One possibility could be the late initiation of therapy. However, the interval between diagnosis and initiation of intravenous therapy was similar in patients who achieved a low-risk profile and those who did not. In addition, the vast majority (79%) of patients in the present series were in the intermediate-risk category with 83% being in FC II or III when intravenous therapy was started. This is consistent with current guideline recommendations.[4,5,7] Still, the 6MWD at the time of treprostinil initiation was higher in patients who reached a low-risk profile at follow-up (438 m vs 297 m, $p = 0.002$), indicating that the likelihood of a favorable response to therapy may be higher in patients with less advanced functional impairment. In

this context, it is noteworthy that previous observational studies have shown a much more impressive therapeutic response when the intravenous prostacyclin therapy was initiated in treatment-naïve patients as part of an upfront combination regimen.[22,23] In contrast, late initiation of intravenous prostacyclin therapy was an independent predictor of a poor outcome in a series from Italy.[24] Taken together, these observations favor early initiation of intravenous therapy, but further studies are needed to better determine when this treatment should be initiated and which patients benefit most.

It is also possible that treprostinil was not optimally dosed as the average dosages used in our study appeared lower than in series by Bartolome and coworkers (median dose in our study, 35 ng/kg/min vs a mean dose of 45 ng/kg/min in the study by Bartolome and coworkers).[21] However, all participating centers titrated treprostinil to the highest individually tolerated dose, and the fact that almost all patients were receiving combinations of other PAH drugs at baseline may have limited the ability to reach higher treprostinil dosages. In addition, the treprostinil doses in patients who reached a low-risk status did not differ significantly from those in patients who did not, which is why it seems unlikely that insufficient treprostinil dosing explains our findings. Age needs to be considered as well, as older patients are less likely to reach a low-risk status than younger patients.[25,26] The median age of the patients in this series was 48 years, which is comparable to other cohorts,[21] but the patients who reached a low-risk profile in this series were younger than the patients who did not (median age, 39 vs 51 years; $p = 0.012$). Given that almost all patients in the current series had been treated with double or triple combinations of PAH drugs prior to the initiation of intravenous treprostinil, we assume that the overall efficacy of intravenous prostacyclin analogues is limited when this treatment is administered in patients who have already exhausted other treatment options.

Our study had several limitations, including the retrospective design (although the data were prospectively captured), the relatively small number of patients, particularly in some of the subgroups of interest, and the lack of a control group of comparable patients not treated with treprostinil. The latter would have been helpful to better determine the effects of intravenous treprostinil as an add-on treatment on transplantation-free survival. It is conceivable that some of the patients, in whom risk category did not improve, experienced clinically relevant benefits. In the absence of a control group, it is impossible to determine such effects. In addition, the majority of patients in our series were categorized as intermediate-risk, both at baseline as well as at follow-up. The ESC/ERS stratification tool provides insufficient risk discrimination in this cohort, and additional variables may help to better determine individual mortality risk and the need for transplantation in these patients. Finally our data should not be extrapolated to other intravenous prostacyclin analogues, most importantly epoprostenol, even though our findings are comparable to the abovementioned study by Bartolome and coworkers who used predominantly epoprostenol.[21]

In summary, our data show that systematic risk assessment within 6−12 months after the initiation of add-on intravenous treprostinil treatment in patients with PAH allows the prediction of the long-term outcome. Patients who reach a low-risk profile have an excellent long-term survival, whereas patients who remain at intermediate or high risk have a median transplant-free survival rate of approximately 2 years. These findings may help guide further treatment decisions, including the timing of listing for lung transplantation.

Disclosure statement

K.M.O. has received speaker fees from Actelion, Bayer, GSK, Pfizer, and United Therapeutics. M.J.R. discloses personal fees from Actelion, Bayer, Mundipharma, Roche, and United Therapeutics/OMT. H.G. discloses personal fees and non-financial support from Actelion, Astra Zeneca, Bayer, BMS, GlaxoSmithKline, Janssen Cilag, Lilly, MSD, Novartis, Pfizer, and United Therapeutics/OMT. H-A.G. discloses personal fees from Actelion, Astra Zeneca, Bayer, GlaxoSmithKline, MSD, Novartis, Pfizer, and United Therapeutics/OMT. R.E. has received speaker fees and honoraria for consultations from Actelion, OMT, Bayer, BMS, GSK, Berlin Chemie, Astra Zeneca, and Boehringer Ingelheim. M.H. has received speaker fees and honoraria for consultations from Actelion, Bayer, GSK, and MSD. The remaining authors have no conflicts of interest to disclose.

Supplementary data

Supplementary data associated with this article can be found in the online version at www.jhltonline.org/.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.healun.2019.05.002.

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