ERJ Express. Published on February 27, 2009 as doi: 10.1183/09031936.00130408

Revision 2 - marked

Long-term outcome with intravenous iloprost in pulmonary arterial hypertension

MM Hoeper,[1] H Gall,[2] HJ Seyfarth,[3] M Halank,[4] HA Ghofrani,[2] J Winkler,[3] H Golpon,[1] KM Olsson,[1] N Nickel,[1] C Opitz,[5] R Ewert,[6]

From the [1]Department of Respiratory Medicine, Hannover Medical School, Hannover, [2]Department of Respiratory Medicine, University of Giessen Lung Center, Giessen, [3]Department of Respiratory Medicine, University of Leipzig, [4]Department of Internal Medicine I, Carl-Gustav-Carus University Dresden, [5]Department of Cardiology, DRK Kliniken Berlin Köpenick, Berlin, and [6]the Department of Cardiology and Respiratory Medicine, University of Greifswald, all in Germany

Correspondence: Marius M. Hoeper, MD, Hannover Medical School, Department of Respiratory Medicine, Carl-Neuberg-Str. 1, 30625 Hannover, Germany. Fax: 49 511 532-8536. E-mail: hoeper.marius@mh-hannover.de

Key words: Hypertension, pulmonary; prostanoids; iloprost; prognosis

Word count body of text: 3,019

Abstract

There is limited data on the long-term efficacy of intravenous iloprost in patients with pulmonary arterial hypertension (PAH).

This retrospective multicenter analysis evaluated the clinical course of patients with PAH treated with intravenous iloprost, in most cases after having received inhaled iloprost as first-line therapy.

Between 1997 and 2001, 79 PAH patients were treated with intravenous iloprost and followed until 2007. These patients had advanced and progressive disease as indicated by a mean pulmonary vascular resistance of 1,533 $dyn \cdot s \cdot cm^{-5}$ at the time of diagnosis and of 1,858 $dyn \cdot s \cdot cm^{-5}$ at the onset of intravenous iloprost therapy, respectively. Introduction of intravenous iloprost therapy resulted in initial hemodynamic and clinical improvement. At the end of the observation period, however, 50 (61%) patients had died and 21 (26%) required lung transplantation. Transplantation-free survival rates at 1, 3, and 5 years were 86%, 59%, and 45%, respectively, after the diagnosis of PAH, and 54%, 31%, and 15%, respectively, after the introduction of intravenous iloprost therapy. Predictors of an adverse outcome at baseline were a low 6 min walk distance and a low mixed-venous oxygen saturation.

In conclusion, despite initial hemodynamic and clinical improvement the overall long-term survival with intravenous iloprost therapy was limited.

Word count abstract: 198

Introduction

The treatment of severe pulmonary arterial hypertension (PAH) has changed substantially during the last couple of years. In the early nineties, intravenous (IV) epoprostenol, a prostacyclin analogue, was the only drug with proven efficacy in this condition and thus, epoprostenol was used first-line in the vast majority of PAH patients [1-3]. Since the mid nineties, non-parenteral treatments were developed and approved for PAH, including endothelin receptor antagonists [4], phosphodiesterase-5 inhibitors [5], and prostanoid analogues [6]. These drugs are now widely used in PAH, especially in patients presenting in functional classes II and III, while intravenous epoprostenol became more of a rescue medication for patients presenting in functional class IV or those deteriorating while receiving less invasive medical therapies [7, 8].

In Germany, epoprostenol has never been approved for PAH and for historical reasons, iloprost has become the standard prostanoid for inhaled and intravenous use in this country, although this drug has also not been approved for IV administration. Intravenous iloprost is also widely used to treat PAH in some other European Countries including the United Kingdom and Spain. When compared with epoprostenol, iloprost has the potential advantages of being more stable in solution and having a longer plasma half-life [9, 10], which makes the use of this drug more convenient and possibly safer. However, it has never been formally studied whether or not iloprost is as efficacious as epoprostenol in PAH and few long-term data with intravenous iloprost have been published [11, 12]. To the best of our knowledge, only two studies have directly compared IV epoprostenol and IV iloprost [13, 14]. Both studies suggested comparable efficacy of epoprostenol and iloprost but these data must be considered preliminary as the two studies were not randomized and limited in size and duration.

As more data on the efficacy of intravenous iloprost are needed, we analyzed the long-term outcome of patients treated with IV iloprost in five German centers specialized in the treatment of PAH.

Methods

Data were retrospectively analyzed from all PAH patients in whom IV iloprost treatment was instituted in the participating centers (university hospitals of Berlin, Dresden, Giessen, Hannover, and Leipzig, all in Germany) between Jan 1st, 1997 and Dec 31st, 2001, i.e. prior to the introduction of endothelin receptor antagonists and phosphodiesterase-5 (PDE-5) inhibitors. Follow-up ended Dec 31st, 2007 so that the outcome of all patients could be determined for a minimum period of 6 years. Inclusion criteria were a diagnosis of PAH and

the introduction of intravenous iloprost treatment at any time during the course of the disease. Patients with other forms of pulmonary hypertension were excluded. This analysis was approved by the institutional review boards of the participating centers. Informed consent was waived according to German regulations for non-interventional, retrospective analyses.

The patients were treated according to the local standards of the enrolment period which included inhaled iloprost and oral anticoagulants as well as oxygen and diuretics based on individual needs. Inhaled iloprost was administered at dosages between 30 and 45 μg per day divided into 6-9 inhalations. There were no predefined criteria for the introduction of intravenous iloprost therapy. All patients were admitted to the hospital for the initiation of this treatment. Iloprost was diluted in normal saline to a total volume of 100 ml and administered intravenously with a portable pump (CADD-1, Deltec) via a port catheter or a Hickman catheter. The medications were prepared under sterile conditions by specialized pharmacists equipped with laminar airflow hoods. Cassettes were changed by the patients every 48 hours. Dosing was left to the discretion of the physician in charge and was guided by drug efficacy and side-effects. Some centers used hemodynamic guidance for the initiation of therapy; in these cases hemodynamic variables immediately prior to intravenous iloprost treatment and at the end of the initial up-titration period were recorded. There were no pre-specified schedules for follow-up right heart catheterizations.

Statistical analysis

Statistical analyses were performed with Excel 2007 and SPSS 16.0. Data are presented as mean ± standard deviation (SD) or median and 95% confidence intervals (CI), as appropriate. Kaplan-Meier plots were used to illustrate overall survival and transplantation-free survival, respectively, and statistical assessments were performed by the log-rank test. Patients undergoing transplantation were censored at that time for the analysis of overall survival. Chi-square analysis was used to compare the observed survival rates at 1, 2, and 3 years with the expected survival rates. Expected survival (IPAH only) was calculated according to the NIH equation [15], with $P(t) = H(t)^{A(x,y,z)}$, with A (x,y,z) = EXP (0.007325x + 0.0526y – 0.3235z) where x is mean pulmonary arterial pressure, y is mean right atrial pressure, and z is cardiac index. The probabilities of survival at 1, 2, and 3 years were calculated as $P(1) = 0.75^A$, $P(2) = 0.65^A$, and $P(3) = 0.55^A$. Univariate and multivariate Cox analyses according to the stepwise forward likelihood ratio method were done to identify risk factors of an adverse outcome (death or lung transplantation) using age, functional class, 6 min walk distance, hemodynamics at the time of diagnosis and at the onset of intravenous iloprost therapy. Differences between hemodynamic parameters at baseline, at the time of initiation of iloprost therapy, after the initial up-titration and during follow-up were assessed with one-way

analysis of variance (ANOVA). Multiple comparisons were made when the F-test was statistically significant. A paired t-test was used to compare the 6 min walk distances prior to intravenous iloprost therapy and 3 months later. P-values < 0.05 were considered statistically significant.

Results

Between Jan 1st, 1997 and Dec 31st, 2001 a total of 480 patients with PAH were treated in the participating centers. Of these patients, 79 (18%) received intravenous iloprost and were eligible for this analysis. The baseline characteristics of the patients under study are shown in Table 1. The clinical courses of some of these patients have been presented in earlier publications [11, 12]. None of the patients in the present series had a positive response to acute vasodilator challenge. Initial treatment included anticoagulation, diuretics and oxygen as needed. Inhaled iloprost was used as first-line therapy in the vast majority (n=75; 95%) of the patients, while only 4 (5%) patients were treated immediately with intravenous iloprost. The interval between the initial diagnosis of PAH and the initiation of intravenous therapy ranged from 0 to 69 months (median, 12 months).

During the observation period, 50 (61%) patients died and 21 (26%) additional patients underwent lung or heart-lung transplantation, resulting in an overall transplantation-free survival of 10%. The median survival from the time of diagnosis was 33 months (range, 0-108 months). The median survival from the initiation of intravenous iloprost was 12 months (range, 0-108 months).

Survival from the initial diagnosis

The probabilities of overall survival, i.e. with censoring patients at the time of lung transplantation, from the time of diagnosis after 1, 2, 3, 4, 5 and 6 years were 86%, 73%, 59%, 46%, 40% and 36% respectively (data not shown). The probabilities of transplantation-free survival from the time of diagnosis after 1, 2, 3, 4, 5 and 6 years were 82%, 65%, 54%, 33%, 26% and 23% respectively (Figure 1).

In the subpopulation of IPAH patients (n=62), transplantation-free survival rates from the time of diagnosis for the IPAH population under study after 1, 2, 3, 4, 5 and 6 years were 86%, 65%, 44%, 32%, 26% and 23% respectively (data not shown).

Predictors of death according to univariate Cox regression analysis were a low 6 min walk distance, a low cardiac index, a high pulmonary vascular resistance and a low mixed venous oxygen saturation at the time of the diagnosis. In the stepwise multivariate analysis the only factors that remained statistically significant were a low 6 min walk distance and a low mixed venous oxygen saturation (Table 2).

Survival from the initiation of intravenous iloprost therapy

Figure 2 shows the outcome of the entire patient population after the introduction of intravenous iloprost therapy. The probabilities of transplantation-free survival from the initiation of intravenous iloprost therapy after 1, 2, 3, 4, 5 and 6 years were 54%, 35%, 31%, 24%, 15% and 13% respectively.

The results were similar for the IPAH subpopulation with transplantation-free survival rates 1, 2, 3, 4, 5 and 6 years after the start of intravenous iloprost of 57%, 37%, 32%, 26%, 18% and 15%, respectively (data not shown). The expected survival rates of these patients after 1, 2 and 3 years calculated with the NIH registry equation based on the hemodynamic parameters obtained immediately before the onset of intravenous iloprost therapy were 58%, 44% and 34%, respectively, i.e. almost identical to the observed survival (non-significant differences at all three time points; data not shown).

A modified hazard analysis with parameters obtained at the time of the initiation of intravenous iloprost therapy (Table 3) revealed similar results as the hazard analysis using parameters at the time of the diagnosis with the difference that NYHA class was now significantly associated with the outcome in the univariate, although not in the multivariate, analysis, whereas the 6 min walk distance was no longer a significant predictor of outcome (statistical power limited due to low numbers because of missing values).

Iloprost dose, hemodynamic effects and exercise tolerance

The dose of iloprost at the time of discharge was 1.8±0.8 ng/kg/min. As shown in Table 4, there was a significant immediate hemodynamic improvement associated with the start of intravenous iloprost with a drop in the pulmonary vascular resistance from 1,965 ± 871 to 1,474 ± 606 $dyn \cdot s \cdot cm^{-5}$ (-25%). Follow-up right heart catheter examinations between 2 and 15 (median, 6) months after initiation of intravenous iloprost were available for 37 patients. At that time, the iloprost dose was 2.6±1.2 ng/kg/min. The pulmonary vascular resistance was

now 1,594 ± 651 $dyn \cdot s \cdot cm^{-5}$, i.e. slightly higher than immediately after the introduction of intravenous iloprost therapy but still substantially lower than before (-19% from baseline).

Functional class was assessed in 72 patients directly before the start of intravenous iloprost and 3 months later and improved by at least one class in 27 patients (38%), was unchanged in 44 patients (61%), and worsened in 1 patient (1%). At the same time measurements of 6 min walk distance were available from 29 patients and showed an increase from 228 ± 114 m to 310 ± 74 m ($p = 0.002$).

Adverse events related to therapy

A total 8 episodes of catheter-related blood stream infections were reported in 6 patients and two of these episodes were directly related to death. However, due to the retrospective nature of this study, underreporting cannot be ruled out. Other side-effects included headache, jaw-pain, leg pain, nausea and diarrhoea but these side-effects were manageable with adaptation of the iloprost dose and did not lead to treatment withdrawals.

Discussion

The present retrospective analysis showed that patients with advanced PAH have a high rate of treatment failure when treated sequentially with inhaled and intravenous iloprost. In this patient population the transplantation-free survival rates from the time of diagnosis after 1, 2, 3, 4, 5 and 6 years were 82%, 65%, 54%, 33%, 26% and 23% respectively. The transplantation-free survival rates after the introduction of intravenous iloprost therapy were 57%, 37%, 32%, 26%, 18% and 15% respectively. At the end of the observation period only 8 out of 79 patients (10%) had survived without transplantation. The predictors of death including a low 6 min walk distance and a low mixed-venous oxygen saturation at the time of diagnosis were in accordance with previous studies [16-19].

What are the explanations for these disturbingly high rates of treatment failure? First of all, the 79 patients under study might have represented a “negative selection” from a much larger population of 480 PAH patients for that they could not be stabilized with inhaled iloprost and conventional therapy. On the other hand, the patients under study were “positively selected” as they had survived from the initial diagnosis to the onset of intravenous iloprost therapy, i.e. a median time of 12 months after the diagnosis of PAH had been made. Both factors created a selection bias into opposite directions and the net effect is unclear.

Beyond any doubt, the patients under study had very severe and aggressive disease as underscored by the hemodynamic data at the time of the initial diagnosis which revealed a mean PVR of >1.500 $dyn \cdot s \cdot cm^{-5}$, a mean right atrial pressure of 10 mmHg, and a mean mixed-venous oxygen saturation of 54%. At the time when intravenous iloprost was started the mean PVR had risen to >1.850 $dyn \cdot s \cdot cm^{-5}$, the mean right atrial pressure was now 13 mmHg, and the mean mixed venous oxygen saturation had dropped to 47% showing that the patients had advanced right heart dysfunction at that time. The introduction of intravenous iloprost therapy resulted in a sustained reduction of the pulmonary vascular resistance (-19% from baseline after 2-15 months). This effect was apparently less pronounced than what has been reported with intravenous epoprostenol by Sitbon et al. (-30% after 3 months) and McLaughlin et al. (-39% after an average treatment time of 17 months) [16, 18]. This difference may be partly explained by the fact that the patients in the present study were pre-treated whereas the patients in the epoprostenol series were treatment-naive. Other factors, however, might also have played a role including the dosing of iloprost as discussed further down below and the lack of a standardized protocol for follow-up catheterizations which could have created another bias in that patients responding less well to therapy might have been more likely to undergo repeated right heart catheterization.

It is interesting and sobering at the same time to see that the introduction of intravenous iloprost treatment was associated with a hemodynamic benefit as well as a substantial improvement in exercise capacity after 3 months of therapy (as indicated by an improvement of at least one functional class in 38% of the patients and an average gain in 6 min walking distance by 82 m) but that the overall outcome of these patients was nevertheless poor.

It could be argued that the poor long-term outcome of the patients in the present study might have been related to the fact that intravenous iloprost treatment was not started at the time of the diagnosis but only when the patients deteriorated while being treated with inhaled iloprost, and therefore too late. There is no way to prove whether or not this assumption is right or wrong. However, the overall survival from the time of diagnosis of the patients under study was comparable to a yet unpublished series of patients treated in the United Kingdom first-line with intravenous iloprost (Corris P et al. personal communication).

Another possible reason for the limited success with intravenous iloprost therapy might have been underdosing. The optimal dose of intravenous iloprost has never been studied but there is probably the same individual variability as seen with epoprostenol [16, 18, 20]. The average dose of iloprost in the present study (2.6 ng/kg/min after a median treatment time of 6 months) was in the same range as the iloprost dose used by Higenbottam et al. in an earlier pilot study (2.1 ng/kg/min after a median treatment time of 7 weeks) [13] but lower than the iloprost dose used in the abovementioned unpublished study from the United Kingdom (3.3 ng/kg/min after 3 months and 4.7 ng/kg/min after 1 year, respectively; Corris P et al. personal

communication). We cannot exclude the possibility that more aggressive dosing might have resulted in better treatment results.

Do the present data suggest that intravenous iloprost might be less efficacious than intravenous epoprostenol? This is certainly the key question. Intravenous epoprostenol remains the only therapy for which a survival benefit has been shown in a randomized controlled clinical trial [1]. That study, however, was an unblinded short-term study of 12-week duration. Long-term survival with intravenous epoprostenol has never been assessed in a randomized controlled fashion and most of the evidence comes from two large series that have been published several years ago [16, 18]. The overall survival rates of the patients in the present study from the time of diagnosis (with censoring patients at the time of transplantation) were similar to those reported with intravenous epoprostenol, but the survival rates on intravenous therapy were considerable lower. All in all, there are too many differences between the present study and the epoprostenol series to allow a fair comparison of both treatments.

Although it is generally accepted that intravenous epoprostenol therapy has a beneficial effect on survival in PAH patients, improved long-term outcome has never been formally proved with any PAH therapy, including intravenous epoprostenol. In fact, looking at the long-term survival with any intravenous prostanoid may raise concerns as to whether these drugs truly slow or halt disease progression since the effect on survival seems most prominent in the first year of treatment, but not thereafter. Given the invasiveness, risks and costs associated with intravenous prostacyclin therapy, more long-term data are certainly needed, but there are several ethical and practical obstacles to conducting randomized controlled long-term trials with intravenous prostanoids. Just looking at the long-term results with intravenous prostanoid therapy indicates that the current options for treating patients with the most advanced forms of PAH remain limited. The best therapeutic approach to patients with the most severe forms of pulmonary hypertension remains unknown although there is emerging data suggesting that the survival of these patients may improve with combination therapy [21, 22]. However, it is likely that the highest chances to improve the outcome of PAH patients lie in early diagnosis and prompt targeted intervention [23].

The present study has some limitations, especially the retrospective design, the heterogeneous patient population, the sequential therapeutic approach, the lack of a control group, and the abundance of missing data, which make the interpretation of the data difficult. The present data should be viewed merely as descriptive and as such they are important as they represent the most valuable source of information on the long-term outcome with this treatment currently available.

In conclusion the use of intravenous iloprost in patients deteriorating while being treated with inhaled iloprost improves hemodynamics but has an unclear effect on the long-term survival of these patients.

Figure legends

Fig 1. Transplantation-free survival from the time of diagnosis of patients with pulmonary arterial hypertension treated with a sequential approach of inhaled and intravenous iloprost (n = 79).

Numbers at risk were n=64, n=51, n=37, n=26, n=20, and n=17 after 1, 2, 3, 4, 5 and 6 years, respectively.

Fig 2. Transplantation-free survival from the onset of intravenous iloprost therapy of patients with pulmonary arterial hypertension treated with a sequential approach of inhaled and intravenous iloprost (n = 79).

Numbers at risk were n=41, n=27, n=24, n=19, n=12, and n=6 after 1, 2, 3, 4, 5 and 6 years, respectively.

Table 1. Characteristics of the patient populations at the time of the diagnosis of PAH and at the onset of intravenous iloprost therapy

	Population under study	
	Time of diagnosis	Onset of IV iloprost
	n = 79	
Female/Male	59/20 (75/25%)	
Age (years)	47 ± 13	48 ± 14
Diagnosis		
IPAH	62 (78%)	
PAH-CTD	10 (13%)	
PAH-CHD	2 (3%)	
PoPH	5 (6%)	
Functional NYHA class III/IV	61/18 (77/23%)	24/49 (33/67%)*
6-min walk distance (m)	287 ± 112	228 ± 114**
Hemodynamics		
RAP (mmHg)	10 ± 6	13 ± 6
PAPm (mmHg)	57 ± 12	61 ± 15
PCWP (mmHg)	8 ± 6	8 ± 3
CO (l/min)	3.0 ± 1.0	2.7 ± 0.8
CI (l/min/m^2)	1.7 ± 0.6	1.5 ± 0.4
PVR (dyn·s·cm^{-5})	1,533 ± 624	1,858 ± 856
SvO_2 (%)	54 ± 11	47 ± 10

Abbreviations: IPAH, idiopathic pulmonary arterial hypertension, PAH-CTD, pulmonary arterial hypertension associated with connective tissue disease; PAH-CHD, pulmonary arterial hypertension associated with congenital heart disease; PoPH, portopulmonary hypertension; NYHA, New York Heart Association; RAP, right atrial pressure; PAPm, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; CO, cardiac output; CI, cardiac index; PVR, pulmonary vascular resistance; SvO_2, mixed-venous oxygen saturation; *n=73 due to missing values; ** n=42 due to missing values.

Table 2. Risk of an adverse outcome (death or lung transplantation) in relation to risk marker measurements at the time of the diagnosis

	Simple model		Multiple model	
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**
Mean RAP (per 1 mmHg ↑)	1.04 (0.99 to 1.1)	0.075		
Cardiac index (per 0.5 l/min/m² ↓)	1.05 (0.99 to 1.1)	0.043		
PVR (per 100 dyn·sec·cm^{-5} ↑)	1.04 (1.0 to 1.08)	0.024		
SvO_2 (per 5% ↓)	1.14 (1.02 to 1.29)	0.026	1.03 (1.03 to 1.53)	0.028
PAPm (per 5mmHg ↑)	1.02 (0.998 to 1.19)	0.056		
6mw (per 20m↓)	1.12 (1.05 to 1.24)	0.001	1.12 (1.05 to 1.21)	0.001
NYHA	1.20 (0.61 to 2.12)	0.589		

Estimated hazard ratios (HR), 95% confidence intervals (CI), and P-values were calculated by simple and stepwise forward Cox regression analyses. Hazard ratios refer to the indicated scales in these variables. RAP denotes right atrial pressure; PVR, pulmonary vascular resistance; SvO_2, mixed-venous oxygen saturation; PAPm, mean pulmonary artery pressure; 6mw, 6 min walk distance.

Table 3. Risk of an adverse outcome (death or lung transplantation) in relation to risk marker measurements at the onset of intravenous iloprost therapy

	Simple model		Multiple model	
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**
Mean RAP (per 1 mmHg ↑)	1.05 (1.0-1.09)	0.042		
Cardiac index (per 0.5 l/min/m² ↓)	1.5 (1.06-2.13)	0.02		
PVR (per 100 dyn·sec·cm^{-5} ↑)	1.02 (0.99-1.05)	0.11		
SvO_2 (per 5% ↓)	1.3 (1.13-1.5)	<0.001	1.1 (1.01-1.2)	0.003
PAPm (per 5mmHg ↑)	1.03 (0.95-1.1)	0.49		
6mwt (per 20m↓)*	1.0 (0.99-1.01)	0.6		
NYHA**	1.7 (1.2-2.8)	0.046		

Estimated hazard ratios (HR), 95% confidence intervals (CI), and P-values were calculated by simple and stepwise forward Cox regression analyses. Hazard ratios refer to the indicated scales in these variables. NYHA denotes New York Heart Association; RAP, right atrial pressure; PVR, pulmonary vascular resistance; SvO_2, mixed-venous oxygen saturation; PAPm, mean pulmonary artery pressure; 6mw, 6 min walk distance; IV, intravenous. *6 mwt data were available only for 42 patients; ** NYHA data were available only for 73 patients.

Table 4. Hemodynamic variables at the time of the diagnosis of PAH, immediately before initiation of intravenous iloprost (baseline) treatment, at the end of the initial up-titration period, and during follow-up (n=37)

	Baseline **A**	**Before start of IV iloprost** **B**	**After dose up-titration** **C**	**Follow-up** **D**
	First right heart catheter Diagnosis of PAH	Immediately before the introduction of IV iloprost†	Initial hemodynamic response to iloprost	Median 6 months (range, 2-15 months) on IV iloprost therapy
Iloprost dose (ng/kg/min)	-	-	1.8±0.8	2.6±1.2
RAP (mmHg)	10 ± 6	13 ± 6	10 ± 5	11 ± 5
PAPm (mmHg)	59 ± 13	63 ± 15	60 ± 15	58 ± 14
PCWP (mmHg)	7 ± 4	8 ± 4	8 ± 4	7 ± 4
CO (l/min)	3.2 ± 1.2	2.7 ± 0.7	3.3 ± 0.8*	2.9 ± 1.1
CI (l/min/m^2)	1.8 ± 0.6	1.5 ± 0.3	1.9 ± 0.5*	1.6 ± 0.5
PVR (dyn·s·cm^{-5})	1,563 ± 602	1,965 ± 871	1,474 ± 606*	1,594 ± 651*
SvO_2 (%)	53 ± 11	46 ± 10	57 ± 10*	53 ± 10*

†The median interval between the first and the second right heart catheterization was 12 months

Abbreviations: RAP, right atrial pressure; PAPm, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; CO, cardiac output; CI, cardiac index; PVR, pulmonary vascular resistance; SvO_2, mixed-venous oxygen saturation. *P < 0.05 vs. B.

References

1. Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, Groves BM, Tapson VF, Bourge RC, Brundage BH, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. *N Engl J Med* 1996: 334(5): 296-302.
2. Badesch DB, Tapson VF, McGoon MD, Brundage BH, Rubin LJ, Wigley FM, Rich S, Barst RJ, Barrett PS, Kral KM, Jobsis MM, Loyd JE, Murali S, Frost A, Girgis R, Bourge RC, Ralph DD, Elliott CG, Hill NS, Langleben D, Schilz RJ, McLaughlin VV, Robbins IM, Groves BM, Shapiro S, Medsger TA, Jr. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial. *Ann Intern Med* 2000: 132(6): 425-434.
3. Rubin LJ. Primary pulmonary hypertension. *N Engl J Med* 1997: 336(2): 111-117.
4. Dupuis J, Hoeper MM. Endothelin receptor antagonists in pulmonary arterial hypertension. *Eur Respir J* 2008: 31: 407-414.
5. Wilkins MR, Wharton J, Grimminger F, Ghofrani HA. Phosphodiesterase inhibitors for the treatment of pulmonary hypertension. *Eur Respir J* 2008: 32(1): 198-209.
6. Olschewski H, Gomberg-Maitland M. Prostacyclin therapies for the treatment of pulmonary arterial hypertension. *Eur Respir J* 2008: 31: 801-901.
7. Galie N, Torbicki A, Barst R, Dartevelle P, Haworth S, Higenbottam T, Olschewski H, Peacock A, Pietra G, Rubin LJ, Simonneau G, Priori SG, Garcia MA, Blanc JJ, Budaj A, Cowie M, Dean V, Deckers J, Burgos EF, Lekakis J, Lindahl B, Mazzotta G, McGregor K, Morais J, Oto A, Smiseth OA, Barbera JA, Gibbs S, Hoeper M, Humbert M, Naeije R, Pepke-Zaba J. Guidelines on diagnosis and treatment of pulmonary arterial hypertension. The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. *Eur Heart J* 2004: 25(24): 2243-2278.
8. Badesch DB, Abman SH, Ahearn GS, Barst RJ, McCrory DC, Simonneau G, McLaughlin VV. Medical therapy for pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest* 2004: 126(1 Suppl): 35S-62S.
9. Goldsmith DR, Wagstaff AJ. Inhaled iloprost: in primary pulmonary hypertension. *Drugs* 2004: 64(7): 763-773; discussion 774-765.
10. Olschewski H, Rohde B, Behr J, Ewert R, Gessler T, Ghofrani HA, Schmehl T. Pharmacodynamics and pharmacokinetics of inhaled iloprost, aerosolized by three different devices, in severe pulmonary hypertension. *Chest* 2003: 124(4): 1294-1304.
11. Hoeper MM, Spiekerkoetter E, Westerkamp V, Gatzke R, Fabel H. Intravenous iloprost for treatment failure of aerosolised iloprost in pulmonary arterial hypertension. *Eur Respir J* 2002: 20(2): 339-343.
12. Ewert R, Opitz CF, Wensel R, Winkler J, Halank M, Felix SB. Continuous intravenous iloprost to revert treatment failure of first-line inhaled iloprost therapy in patients with idiopathic pulmonary arterial hypertension. *Clin Res Cardiol* 2007: 96(4): 211-217.
13. Higenbottam TW, Butt AY, Dinh-Xaun AT, Takao M, Cremona G, Akamine S. Treatment of pulmonary hypertension with the continuous infusion of a prostacyclin analogue, iloprost. *Heart* 1998: 79(2): 175-179.
14. Higenbottam T, Butt AY, McMahon A, Westerbeck R, Sharples L. Long-term intravenous prostaglandin (epoprostenol or iloprost) for treatment of severe pulmonary hypertension. *Heart* 1998: 80(2): 151-155.
15. D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Kernis JT, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med* 1991: 115(5): 343-349.

16. McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. *Circulation* 2002: 106(12): 1477-1482.
17. McLaughlin VV, Sitbon O, Badesch DB, Barst RJ, Black C, Galie N, Rainisio M, Simonneau G, Rubin LJ. Survival with first-line bosentan in patients with primary pulmonary hypertension. *Eur Respir J* 2005: 25(2): 244-249.
18. Sitbon O, Humbert M, Nunes H, Parent F, Garcia G, Herve P, Rainisio M, Simonneau G. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. *J Am Coll Cardiol* 2002: 40(4): 780-788.
19. Provencher S, Sitbon O, Humbert M, Cabrol S, Jais X, Simonneau G. Long-term outcome with first-line bosentan therapy in idiopathic pulmonary arterial hypertension. *Eur Heart J* 2006: 27(5): 589-595.
20. Rich S, McLaughlin VV. The effects of chronic prostacyclin therapy on cardiac output and symptoms in primary pulmonary hypertension. *J Am Coll Cardiol* 1999: 34(4): 1184-1187.
21. Hoeper MM, Markevych I, Spiekerkoetter E, Welte T, Niedermeyer J. Goal-oriented treatment and combination therapy for pulmonary arterial hypertension. *Eur Respir J* 2005: 26(5): 858-863.
22. Simonneau G, Rubin LJ, Galie N, Barst RJ, Fleming TR, Frost AE, Engel PJ, Kramer MR, Burgess G, Collings L, Cossons N, Sitbon O, Badesch DB. Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: a randomized trial. *Ann Intern Med* 2008: 149(8): 521-530.
23. Galie N, Rubin L, Hoeper M, Jansa P, Al-Hiti H, Meyer G, Chiossi E, Kusic-Pajic A, Simonneau G. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. *Lancet* 2008: 371(9630): 2093-2100.

Long-term outcome with intravenous iloprost in pulmonary arterial hypertension

MM Hoeper,[1] H Gall,[2] HJ Seyfarth,[3] M Halank,[4] HA Ghofrani,[2] J Winkler,[3] H Golpon,[1] KM Olsson,[1] N Nickel,[1] C Opitz,[5] R Ewert,[6]

From the [1]Department of Respiratory Medicine, Hannover Medical School, Hannover, [2]Department of Respiratory Medicine, University of Giessen Lung Center, Giessen, [3]Department of Respiratory Medicine, University of Leipzig, [4]Department of Internal Medicine I, Carl-Gustav-Carus University Dresden, [5]Department of Cardiology, DRK Kliniken Berlin Köpenick, Berlin, and [6]the Department of Cardiology and Respiratory Medicine, University of Greifswald, all in Germany

Correspondence: Marius M. Hoeper, MD, Hannover Medical School, Department of Respiratory Medicine, Carl-Neuberg-Str. 1, 30625 Hannover, Germany. Fax: 49 511 532-8536. E-mail: hoeper.marius@mh-hannover.de

Key words: Hypertension, pulmonary; prostanoids; iloprost; prognosis

Word count body of text: 3,019

Abstract

There is limited data on the long-term efficacy of intravenous iloprost in patients with pulmonary arterial hypertension (PAH).

This retrospective multicenter analysis evaluated the clinical course of patients with PAH treated with intravenous iloprost, in most cases after having received inhaled iloprost as first-line therapy.

Between 1997 and 2001, 79 PAH patients were treated with intravenous iloprost and followed until 2007. These patients had advanced and progressive disease as indicated by a mean pulmonary vascular resistance of 1,533 $dyn \cdot s \cdot cm^{-5}$ at the time of diagnosis and of 1,858 $dyn \cdot s \cdot cm^{-5}$ at the onset of intravenous iloprost therapy, respectively. Introduction of intravenous iloprost therapy resulted in initial hemodynamic and clinical improvement. At the end of the observation period, however, 50 (61%) patients had died and 21 (26%) required lung transplantation. Transplantation-free survival rates at 1, 3, and 5 years were 86%, 59%, and 45%, respectively, after the diagnosis of PAH, and 54%, 31%, and 15%, respectively, after the introduction of intravenous iloprost therapy. Predictors of an adverse outcome at baseline were a low 6 min walk distance and a low mixed-venous oxygen saturation.

In conclusion, despite initial hemodynamic and clinical improvement the overall long-term survival with intravenous iloprost therapy was limited.

Word count abstract: 198

Introduction

The treatment of severe pulmonary arterial hypertension (PAH) has changed substantially during the last couple of years. In the early nineties, intravenous (IV) epoprostenol, a prostacyclin analogue, was the only drug with proven efficacy in this condition and thus, epoprostenol was used first-line in the vast majority of PAH patients [1-3]. Since the mid nineties, non-parenteral treatments were developed and approved for PAH, including endothelin receptor antagonists [4], phosphodiesterase-5 inhibitors [5], and prostanoid analogues [6]. These drugs are now widely used in PAH, especially in patients presenting in functional classes II and III, while intravenous epoprostenol became more of a rescue medication for patients presenting in functional class IV or those deteriorating while receiving less invasive medical therapies [7, 8].

In Germany, epoprostenol has never been approved for PAH and for historical reasons, iloprost has become the standard prostanoid for inhaled and intravenous use in this country, although this drug has also not been approved for IV administration. Intravenous iloprost is also widely used to treat PAH in some other European Countries including the United Kingdom and Spain. When compared with epoprostenol, iloprost has the potential advantages of being more stable in solution and having a longer plasma half-life [9, 10], which makes the use of this drug more convenient and possibly safer. However, it has never been formally studied whether or not iloprost is as efficacious as epoprostenol in PAH and few long-term data with intravenous iloprost have been published [11, 12]. To the best of our knowledge, only two studies have directly compared IV epoprostenol and IV iloprost [13, 14]. Both studies suggested comparable efficacy of epoprostenol and iloprost but these data must be considered preliminary as the two studies were not randomized and limited in size and duration.

As more data on the efficacy of intravenous iloprost are needed, we analyzed the long-term outcome of patients treated with IV iloprost in five German centers specialized in the treatment of PAH.

Methods

Data were retrospectively analyzed from all PAH patients in whom IV iloprost treatment was instituted in the participating centers (university hospitals of Berlin, Dresden, Giessen, Hannover, and Leipzig, all in Germany) between Jan 1st, 1997 and Dec 31st, 2001, i.e. prior to the introduction of endothelin receptor antagonists and phosphodiesterase-5 (PDE-5) inhibitors. Follow-up ended Dec 31st, 2007 so that the outcome of all patients could be determined for a minimum period of 6 years. Inclusion criteria were a diagnosis of PAH and

the introduction of intravenous iloprost treatment at any time during the course of the disease. Patients with other forms of pulmonary hypertension were excluded. This analysis was approved by the institutional review boards of the participating centers. Informed consent was waived according to German regulations for non-interventional, retrospective analyses.

The patients were treated according to the local standards of the enrolment period which included inhaled iloprost and oral anticoagulants as well as oxygen and diuretics based on individual needs. Inhaled iloprost was administered at dosages between 30 and 45 μg per day divided into 6-9 inhalations. There were no predefined criteria for the introduction of intravenous iloprost therapy. All patients were admitted to the hospital for the initiation of this treatment. Iloprost was diluted in normal saline to a total volume of 100 ml and administered intravenously with a portable pump (CADD-1, Deltec) via a port catheter or a Hickman catheter. The medications were prepared under sterile conditions by specialized pharmacists equipped with laminar airflow hoods. Cassettes were changed by the patients every 48 hours. Dosing was left to the discretion of the physician in charge and was guided by drug efficacy and side-effects. Some centers used hemodynamic guidance for the initiation of therapy; in these cases hemodynamic variables immediately prior to intravenous iloprost treatment and at the end of the initial up-titration period were recorded. There were no pre-specified schedules for follow-up right heart catheterizations.

Statistical analysis

Statistical analyses were performed with Excel 2007 and SPSS 16.0. Data are presented as mean ± standard deviation (SD) or median and 95% confidence intervals (CI), as appropriate. Kaplan-Meier plots were used to illustrate overall survival and transplantation-free survival, respectively, and statistical assessments were performed by the log-rank test. Patients undergoing transplantation were censored at that time for the analysis of overall survival. Chi-square analysis was used to compare the observed survival rates at 1, 2, and 3 years with the expected survival rates. Expected survival (IPAH only) was calculated according to the NIH equation [15], with $P(t) = H(t)^{A(x,y,z)}$, with A (x,y,z) = EXP (0.007325x + 0.0526y – 0.3235z) where x is mean pulmonary arterial pressure, y is mean right atrial pressure, and z is cardiac index. The probabilities of survival at 1, 2, and 3 years were calculated as $P(1) = 0.75^{A}$, $P(2) = 0.65^{A}$, and $P(3) = 0.55^{A}$. Univariate and multivariate Cox analyses according to the stepwise forward likelihood ratio method were done to identify risk factors of an adverse outcome (death or lung transplantation) using age, functional class, 6 min walk distance, hemodynamics at the time of diagnosis and at the onset of intravenous iloprost therapy. Differences between hemodynamic parameters at baseline, at the time of initiation of iloprost therapy, after the initial up-titration and during follow-up were assessed with one-way

analysis of variance (ANOVA). Multiple comparisons were made when the F-test was statistically significant. A paired t-test was used to compare the 6 min walk distances prior to intravenous iloprost therapy and 3 months later. P-values < 0.05 were considered statistically significant.

Results

Between Jan 1st, 1997 and Dec 31st, 2001 a total of 480 patients with PAH were treated in the participating centers. Of these patients, 79 (18%) received intravenous iloprost and were eligible for this analysis. The baseline characteristics of the patients under study are shown in Table 1. The clinical courses of some of these patients have been presented in earlier publications [11, 12]. None of the patients in the present series had a positive response to acute vasodilator challenge. Initial treatment included anticoagulation, diuretics and oxygen as needed. Inhaled iloprost was used as first-line therapy in the vast majority (n=75; 95%) of the patients, while only 4 (5%) patients were treated immediately with intravenous iloprost. The interval between the initial diagnosis of PAH and the initiation of intravenous therapy ranged from 0 to 69 months (median, 12 months).

During the observation period, 50 (61%) patients died and 21 (26%) additional patients underwent lung or heart-lung transplantation, resulting in an overall transplantation-free survival of 10%. The median survival from the time of diagnosis was 33 months (range, 0-108 months). The median survival from the initiation of intravenous iloprost was 12 months (range, 0-108 months).

Survival from the initial diagnosis

The probabilities of overall survival, i.e. with censoring patients at the time of lung transplantation, from the time of diagnosis after 1, 2, 3, 4, 5 and 6 years were 86%, 73%, 59%, 46%, 40% and 36% respectively (data not shown). The probabilities of transplantation-free survival from the time of diagnosis after 1, 2, 3, 4, 5 and 6 years were 82%, 65%, 54%, 33%, 26% and 23% respectively (Figure 1).

In the subpopulation of IPAH patients (n=62), transplantation-free survival rates from the time of diagnosis for the IPAH population under study after 1, 2, 3, 4, 5 and 6 years were 86%, 65%, 44%, 32%, 26% and 23% respectively (data not shown).

Predictors of death according to univariate Cox regression analysis were a low 6 min walk distance, a low cardiac index, a high pulmonary vascular resistance and a low mixed venous oxygen saturation at the time of the diagnosis. In the stepwise multivariate analysis the only factors that remained statistically significant were a low 6 min walk distance and a low mixed venous oxygen saturation (Table 2).

Survival from the initiation of intravenous iloprost therapy

Figure 2 shows the outcome of the entire patient population after the introduction of intravenous iloprost therapy. The probabilities of transplantation-free survival from the initiation of intravenous iloprost therapy after 1, 2, 3, 4, 5 and 6 years were 54%, 35%, 31%, 24%, 15% and 13% respectively.

The results were similar for the IPAH subpopulation with transplantation-free survival rates 1, 2, 3, 4, 5 and 6 years after the start of intravenous iloprost of 57%, 37%, 32%, 26%, 18% and 15%, respectively (data not shown). The expected survival rates of these patients after 1, 2 and 3 years calculated with the NIH registry equation based on the hemodynamic parameters obtained immediately before the onset of intravenous iloprost therapy were 58%, 44% and 34%, respectively, i.e. almost identical to the observed survival (non-significant differences at all three time points; data not shown).

A modified hazard analysis with parameters obtained at the time of the initiation of intravenous iloprost therapy (Table 3) revealed similar results as the hazard analysis using parameters at the time of the diagnosis with the difference that NYHA class was now significantly associated with the outcome in the univariate, although not in the multivariate, analysis, whereas the 6 min walk distance was no longer a significant predictor of outcome (statistical power limited due to low numbers because of missing values).

Iloprost dose, hemodynamic effects and exercise tolerance

The dose of iloprost at the time of discharge was 1.8±0.8 ng/kg/min. As shown in Table 4, there was a significant immediate hemodynamic improvement associated with the start of intravenous iloprost with a drop in the pulmonary vascular resistance from 1,965 ± 871 to 1,474 ± 606 $dyn \cdot s \cdot cm^{-5}$ (-25%). Follow-up right heart catheter examinations between 2 and 15 (median, 6) months after initiation of intravenous iloprost were available for 37 patients. At that time, the iloprost dose was 2.6±1.2 ng/kg/min. The pulmonary vascular resistance was

now 1,594 ± 651 $dyn \cdot s \cdot cm^{-5}$, i.e. slightly higher than immediately after the introduction of intravenous iloprost therapy but still substantially lower than before (-19% from baseline).

Functional class was assessed in 72 patients directly before the start of intravenous iloprost and 3 months later and improved by at least one class in 27 patients (38%), was unchanged in 44 patients (61%), and worsened in 1 patient (1%). At the same time measurements of 6 min walk distance were available from 29 patients and showed an increase from 228 ± 114 m to 310 ± 74 m ($p = 0.002$).

Adverse events related to therapy

A total 8 episodes of catheter-related blood stream infections were reported in 6 patients and two of these episodes were directly related to death. However, due to the retrospective nature of this study, underreporting cannot be ruled out. Other side-effects included headache, jaw-pain, leg pain, nausea and diarrhoea but these side-effects were manageable with adaptation of the iloprost dose and did not lead to treatment withdrawals.

Discussion

The present retrospective analysis showed that patients with advanced PAH have a high rate of treatment failure when treated sequentially with inhaled and intravenous iloprost. In this patient population the transplantation-free survival rates from the time of diagnosis after 1, 2, 3, 4, 5 and 6 years were 82%, 65%, 54%, 33%, 26% and 23% respectively. The transplantation-free survival rates after the introduction of intravenous iloprost therapy were 57%, 37%, 32%, 26%, 18% and 15% respectively. At the end of the observation period only 8 out of 79 patients (10%) had survived without transplantation. The predictors of death including a low 6 min walk distance and a low mixed-venous oxygen saturation at the time of diagnosis were in accordance with previous studies [16-19].

What are the explanations for these disturbingly high rates of treatment failure? First of all, the 79 patients under study might have represented a “negative selection” from a much larger population of 480 PAH patients for that they could not be stabilized with inhaled iloprost and conventional therapy. On the other hand, the patients under study were “positively selected” as they had survived from the initial diagnosis to the onset of intravenous iloprost therapy, i.e. a median time of 12 months after the diagnosis of PAH had been made. Both factors created a selection bias into opposite directions and the net effect is unclear.

Beyond any doubt, the patients under study had very severe and aggressive disease as underscored by the hemodynamic data at the time of the initial diagnosis which revealed a mean PVR of >1.500 $dyn \cdot s \cdot cm^{-5}$, a mean right atrial pressure of 10 mmHg, and a mean mixed-venous oxygen saturation of 54%. At the time when intravenous iloprost was started the mean PVR had risen to >1.850 $dyn \cdot s \cdot cm^{-5}$, the mean right atrial pressure was now 13 mmHg, and the mean mixed venous oxygen saturation had dropped to 47% showing that the patients had advanced right heart dysfunction at that time. The introduction of intravenous iloprost therapy resulted in a sustained reduction of the pulmonary vascular resistance (-19% from baseline after 2-15 months). This effect was apparently less pronounced than what has been reported with intravenous epoprostenol by Sitbon et al. (-30% after 3 months) and McLaughlin et al. (-39% after an average treatment time of 17 months) [16, 18]. This difference may be partly explained by the fact that the patients in the present study were pre-treated whereas the patients in the epoprostenol series were treatment-naive. Other factors, however, might also have played a role including the dosing of iloprost as discussed further down below and the lack of a standardized protocol for follow-up catheterizations which could have created another bias in that patients responding less well to therapy might have been more likely to undergo repeated right heart catheterization.

It is interesting and sobering at the same time to see that the introduction of intravenous iloprost treatment was associated with a hemodynamic benefit as well as a substantial improvement in exercise capacity after 3 months of therapy (as indicated by an improvement of at least one functional class in 38% of the patients and an average gain in 6 min walking distance by 82 m) but that the overall outcome of these patients was nevertheless poor.

It could be argued that the poor long-term outcome of the patients in the present study might have been related to the fact that intravenous iloprost treatment was not started at the time of the diagnosis but only when the patients deteriorated while being treated with inhaled iloprost, and therefore too late. There is no way to prove whether or not this assumption is right or wrong. However, the overall survival from the time of diagnosis of the patients under study was comparable to a yet unpublished series of patients treated in the United Kingdom first-line with intravenous iloprost (Corris P et al. personal communication).

Another possible reason for the limited success with intravenous iloprost therapy might have been underdosing. The optimal dose of intravenous iloprost has never been studied but there is probably the same individual variability as seen with epoprostenol [16, 18, 20]. The average dose of iloprost in the present study (2.6 ng/kg/min after a median treatment time of 6 months) was in the same range as the iloprost dose used by Higenbottam et al. in an earlier pilot study (2.1 ng/kg/min after a median treatment time of 7 weeks) [13] but lower than the iloprost dose used in the abovementioned unpublished study from the United Kingdom (3.3 ng/kg/min after 3 months and 4.7 ng/kg/min after 1 year, respectively; Corris P et al. personal

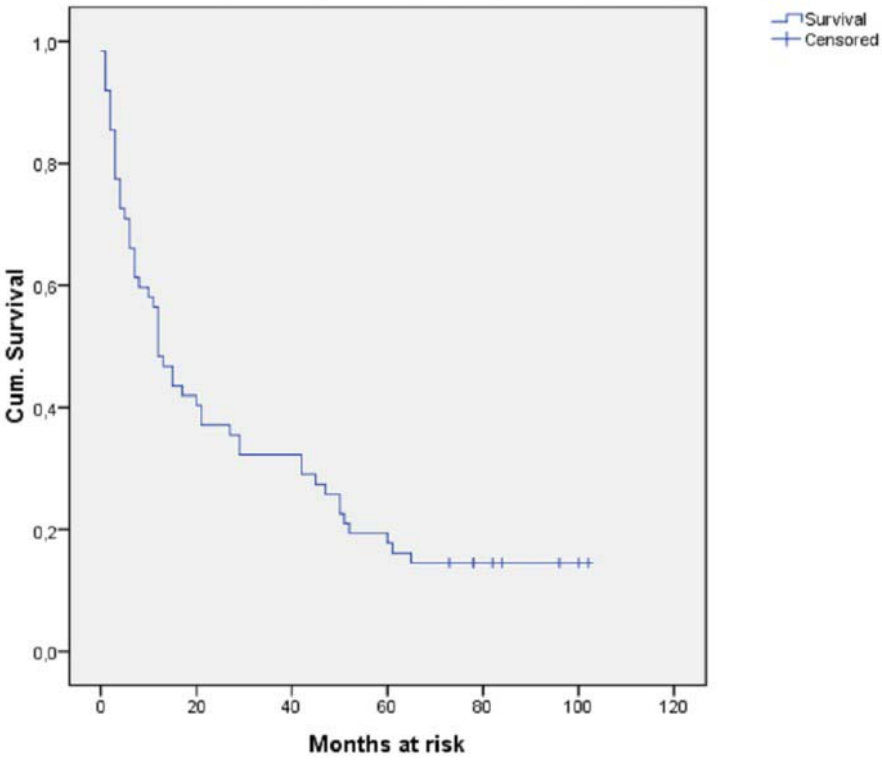
communication). We cannot exclude the possibility that more aggressive dosing might have resulted in better treatment results.

Do the present data suggest that intravenous iloprost might be less efficacious than intravenous epoprostenol? This is certainly the key question. Intravenous epoprostenol remains the only therapy for which a survival benefit has been shown in a randomized controlled clinical trial [1]. That study, however, was an unblinded short-term study of 12-week duration. Long-term survival with intravenous epoprostenol has never been assessed in a randomized controlled fashion and most of the evidence comes from two large series that have been published several years ago [16, 18]. The overall survival rates of the patients in the present study from the time of diagnosis (with censoring patients at the time of transplantation) were similar to those reported with intravenous epoprostenol, but the survival rates on intravenous therapy were considerable lower. All in all, there are too many differences between the present study and the epoprostenol series to allow a fair comparison of both treatments.

Although it is generally accepted that intravenous epoprostenol therapy has a beneficial effect on survival in PAH patients, improved long-term outcome has never been formally proved with any PAH therapy, including intravenous epoprostenol. In fact, looking at the long-term survival with any intravenous prostanoid may raise concerns as to whether these drugs truly slow or halt disease progression since the effect on survival seems most prominent in the first year of treatment, but not thereafter. Given the invasiveness, risks and costs associated with intravenous prostacyclin therapy, more long-term data are certainly needed, but there are several ethical and practical obstacles to conducting randomized controlled long-term trials with intravenous prostanoids. Just looking at the long-term results with intravenous prostanoid therapy indicates that the current options for treating patients with the most advanced forms of PAH remain limited. The best therapeutic approach to patients with the most severe forms of pulmonary hypertension remains unknown although there is emerging data suggesting that the survival of these patients may improve with combination therapy [21, 22]. However, it is likely that the highest chances to improve the outcome of PAH patients lie in early diagnosis and prompt targeted intervention [23].

The present study has some limitations, especially the retrospective design, the heterogeneous patient population, the sequential therapeutic approach, the lack of a control group, and the abundance of missing data, which make the interpretation of the data difficult. The present data should be viewed merely as descriptive and as such they are important as they represent the most valuable source of information on the long-term outcome with this treatment currently available.

In conclusion the use of intravenous iloprost in patients deteriorating while being treated with inhaled iloprost improves hemodynamics but has an unclear effect on the long-term survival of these patients.



ıerapy of patients

ı of inhaled and

4, 5 and 6 years,

Table 1. Characteristics of the patient populations at the time of the diagnosis of PAH and at the onset of intravenous iloprost therapy

	Population under study	
	Time of diagnosis	Onset of IV iloprost
	n = 79	
Female/Male	59/20 (75/25%)	
Age (years)	47 ± 13	48 ± 14
Diagnosis		
IPAH	62 (78%)	
PAH-CTD	10 (13%)	
PAH-CHD	2 (3%)	
PoPH	5 (6%)	
Functional NYHA class III/IV	61/18 (77/23%)	24/49 (33/67%)*
6-min walk distance (m)	287 ± 112	228 ± 114**
Hemodynamics		
RAP (mmHg)	10 ± 6	13 ± 6
PAPm (mmHg)	57 ± 12	61 ± 15
PCWP (mmHg)	8 ± 6	8 ± 3
CO (l/min)	3.0 ± 1.0	2.7 ± 0.8
CI (l/min/m^2)	1.7 ± 0.6	1.5 ± 0.4
PVR (dyn·s·cm^{-5})	1,533 ± 624	1,858 ± 856
SvO_2 (%)	54 ± 11	47 ± 10

Abbreviations: IPAH, idiopathic pulmonary arterial hypertension, PAH-CTD, pulmonary arterial hypertension associated with connective tissue disease; PAH-CHD, pulmonary arterial hypertension associated with congenital heart disease; PoPH, portopulmonary hypertension; NYHA, New York Heart Association; RAP, right atrial pressure; PAPm, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; CO, cardiac output; CI, cardiac index; PVR, pulmonary vascular resistance; SvO_2, mixed-venous oxygen saturation; *n=73 due to missing values; ** n=42 due to missing values.

Table 2. Risk of an adverse outcome (death or lung transplantation) in relation to risk marker measurements at the time of the diagnosis

	Simple model		Multiple model	
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**
Mean RAP (per 1 mmHg ↑)	1.04 (0.99 to 1.1)	0.075		
Cardiac index (per 0.5 l/min/m² ↓)	1.05 (0.99 to 1.1)	0.043		
PVR (per 100 dyn·sec·cm^{-5} ↑)	1.04 (1.0 to 1.08)	0.024		
SvO_2 (per 5% ↓)	1.14 (1.02 to 1.29)	0.026	1.03 (1.03 to 1.53)	0.028
PAPm (per 5mmHg ↑)	1.02 (0.998 to 1.19)	0.056		
6mw (per 20m↓)	1.12 (1.05 to 1.24)	0.001	1.12 (1.05 to 1.21)	0.001
NYHA	1.20 (0.61 to 2.12)	0.589		

Estimated hazard ratios (HR), 95% confidence intervals (CI), and P-values were calculated by simple and stepwise forward Cox regression analyses. Hazard ratios refer to the indicated scales in these variables. RAP denotes right atrial pressure; PVR, pulmonary vascular resistance; SvO_2, mixed-venous oxygen saturation; PAPm, mean pulmonary artery pressure; 6mw, 6 min walk distance.

Table 3. Risk of an adverse outcome (death or lung transplantation) in relation to risk marker measurements at the onset of intravenous iloprost therapy

	Simple model		Multiple model	
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**
Mean RAP (per 1 mmHg ↑)	1.05 (1.0-1.09)	0.042		
Cardiac index (per 0.5 l/min/m² ↓)	1.5 (1.06-2.13)	0.02		
PVR (per 100 dyn·sec·cm^{-5} ↑)	1.02 (0.99-1.05)	0.11		
SvO_2 (per 5% ↓)	1.3 (1.13-1.5)	<0.001	1.1 (1.01-1.2)	0.003
PAPm (per 5mmHg ↑)	1.03 (0.95-1.1)	0.49		
6mwt (per 20m↓)*	1.0 (0.99-1.01)	0.6		
NYHA**	1.7 (1.2-2.8)	0.046		

Estimated hazard ratios (HR), 95% confidence intervals (CI), and P-values were calculated by simple and stepwise forward Cox regression analyses. Hazard ratios refer to the indicated scales in these variables. NYHA denotes New York Heart Association; RAP, right atrial pressure; PVR, pulmonary vascular resistance; SvO_2, mixed-venous oxygen saturation; PAPm, mean pulmonary artery pressure; 6mw, 6 min walk distance; IV, intravenous. *6 mwt data were available only for 42 patients; ** NYHA data were available only for 73 patients.

Table 4. Hemodynamic variables at the time of the diagnosis of PAH, immediately before initiation of intravenous iloprost (baseline) treatment, at the end of the initial up-titration period, and during follow-up (n=37)

	Baseline **A**	**Before start of IV iloprost** **B**	**After dose up-titration** **C**	**Follow-up** **D**
	First right heart catheter Diagnosis of PAH	Immediately before the introduction of IV iloprost†	Initial hemodynamic response to iloprost	Median 6 months (range, 2-15 months) on IV iloprost therapy
Iloprost dose (ng/kg/min)	-	-	1.8±0.8	2.6±1.2
RAP (mmHg)	10 ± 6	13 ± 6	10 ± 5	11 ± 5
PAPm (mmHg)	59 ± 13	63 ± 15	60 ± 15	58 ± 14
PCWP (mmHg)	7 ± 4	8 ± 4	8 ± 4	7 ± 4
CO (l/min)	3.2 ± 1.2	2.7 ± 0.7	3.3 ± 0.8*	2.9 ± 1.1
CI (l/min/m^2)	1.8 ± 0.6	1.5 ± 0.3	1.9 ± 0.5*	1.6 ± 0.5
PVR (dyn·s·cm^{-5})	1,563 ± 602	1,965 ± 871	1,474 ± 606*	1,594 ± 651*
SvO_2 (%)	53 ± 11	46 ± 10	57 ± 10*	53 ± 10*

†The median interval between the first and the second right heart catheterization was 12 months

Abbreviations: RAP, right atrial pressure; PAPm, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; CO, cardiac output; CI, cardiac index; PVR, pulmonary vascular resistance; SvO_2, mixed-venous oxygen saturation. *P < 0.05 vs. B.

References

1. Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, Groves BM, Tapson VF, Bourge RC, Brundage BH, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. *N Engl J Med* 1996: 334(5): 296-302.
2. Badesch DB, Tapson VF, McGoon MD, Brundage BH, Rubin LJ, Wigley FM, Rich S, Barst RJ, Barrett PS, Kral KM, Jobsis MM, Loyd JE, Murali S, Frost A, Girgis R, Bourge RC, Ralph DD, Elliott CG, Hill NS, Langleben D, Schilz RJ, McLaughlin VV, Robbins IM, Groves BM, Shapiro S, Medsger TA, Jr. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial. *Ann Intern Med* 2000: 132(6): 425-434.
3. Rubin LJ. Primary pulmonary hypertension. *N Engl J Med* 1997: 336(2): 111-117.
4. Dupuis J, Hoeper MM. Endothelin receptor antagonists in pulmonary arterial hypertension. *Eur Respir J* 2008: 31: 407-414.
5. Wilkins MR, Wharton J, Grimminger F, Ghofrani HA. Phosphodiesterase inhibitors for the treatment of pulmonary hypertension. *Eur Respir J* 2008: 32(1): 198-209.
6. Olschewski H, Gomberg-Maitland M. Prostacyclin therapies for the treatment of pulmonary arterial hypertension. *Eur Respir J* 2008: 31: 801-901.
7. Galie N, Torbicki A, Barst R, Dartevelle P, Haworth S, Higenbottam T, Olschewski H, Peacock A, Pietra G, Rubin LJ, Simonneau G, Priori SG, Garcia MA, Blanc JJ, Budaj A, Cowie M, Dean V, Deckers J, Burgos EF, Lekakis J, Lindahl B, Mazzotta G, McGregor K, Morais J, Oto A, Smiseth OA, Barbera JA, Gibbs S, Hoeper M, Humbert M, Naeije R, Pepke-Zaba J. Guidelines on diagnosis and treatment of pulmonary arterial hypertension. The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. *Eur Heart J* 2004: 25(24): 2243-2278.
8. Badesch DB, Abman SH, Ahearn GS, Barst RJ, McCrory DC, Simonneau G, McLaughlin VV. Medical therapy for pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest* 2004: 126(1 Suppl): 35S-62S.
9. Goldsmith DR, Wagstaff AJ. Inhaled iloprost: in primary pulmonary hypertension. *Drugs* 2004: 64(7): 763-773; discussion 774-765.
10. Olschewski H, Rohde B, Behr J, Ewert R, Gessler T, Ghofrani HA, Schmehl T. Pharmacodynamics and pharmacokinetics of inhaled iloprost, aerosolized by three different devices, in severe pulmonary hypertension. *Chest* 2003: 124(4): 1294-1304.
11. Hoeper MM, Spiekerkoetter E, Westerkamp V, Gatzke R, Fabel H. Intravenous iloprost for treatment failure of aerosolised iloprost in pulmonary arterial hypertension. *Eur Respir J* 2002: 20(2): 339-343.
12. Ewert R, Opitz CF, Wensel R, Winkler J, Halank M, Felix SB. Continuous intravenous iloprost to revert treatment failure of first-line inhaled iloprost therapy in patients with idiopathic pulmonary arterial hypertension. *Clin Res Cardiol* 2007: 96(4): 211-217.
13. Higenbottam TW, Butt AY, Dinh-Xaun AT, Takao M, Cremona G, Akamine S. Treatment of pulmonary hypertension with the continuous infusion of a prostacyclin analogue, iloprost. *Heart* 1998: 79(2): 175-179.
14. Higenbottam T, Butt AY, McMahon A, Westerbeck R, Sharples L. Long-term intravenous prostaglandin (epoprostenol or iloprost) for treatment of severe pulmonary hypertension. *Heart* 1998: 80(2): 151-155.
15. D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Kernis JT, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med* 1991: 115(5): 343-349.

16. McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. *Circulation* 2002: 106(12): 1477-1482.
17. McLaughlin VV, Sitbon O, Badesch DB, Barst RJ, Black C, Galie N, Rainisio M, Simonneau G, Rubin LJ. Survival with first-line bosentan in patients with primary pulmonary hypertension. *Eur Respir J* 2005: 25(2): 244-249.
18. Sitbon O, Humbert M, Nunes H, Parent F, Garcia G, Herve P, Rainisio M, Simonneau G. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. *J Am Coll Cardiol* 2002: 40(4): 780-788.
19. Provencher S, Sitbon O, Humbert M, Cabrol S, Jais X, Simonneau G. Long-term outcome with first-line bosentan therapy in idiopathic pulmonary arterial hypertension. *Eur Heart J* 2006: 27(5): 589-595.
20. Rich S, McLaughlin VV. The effects of chronic prostacyclin therapy on cardiac output and symptoms in primary pulmonary hypertension. *J Am Coll Cardiol* 1999: 34(4): 1184-1187.
21. Hoeper MM, Markevych I, Spiekerkoetter E, Welte T, Niedermeyer J. Goal-oriented treatment and combination therapy for pulmonary arterial hypertension. *Eur Respir J* 2005: 26(5): 858-863.
22. Simonneau G, Rubin LJ, Galie N, Barst RJ, Fleming TR, Frost AE, Engel PJ, Kramer MR, Burgess G, Collings L, Cossons N, Sitbon O, Badesch DB. Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: a randomized trial. *Ann Intern Med* 2008: 149(8): 521-530.
23. Galie N, Rubin L, Hoeper M, Jansa P, Al-Hiti H, Meyer G, Chiossi E, Kusic-Pajic A, Simonneau G. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. *Lancet* 2008: 371(9630): 2093-2100.

Figure1

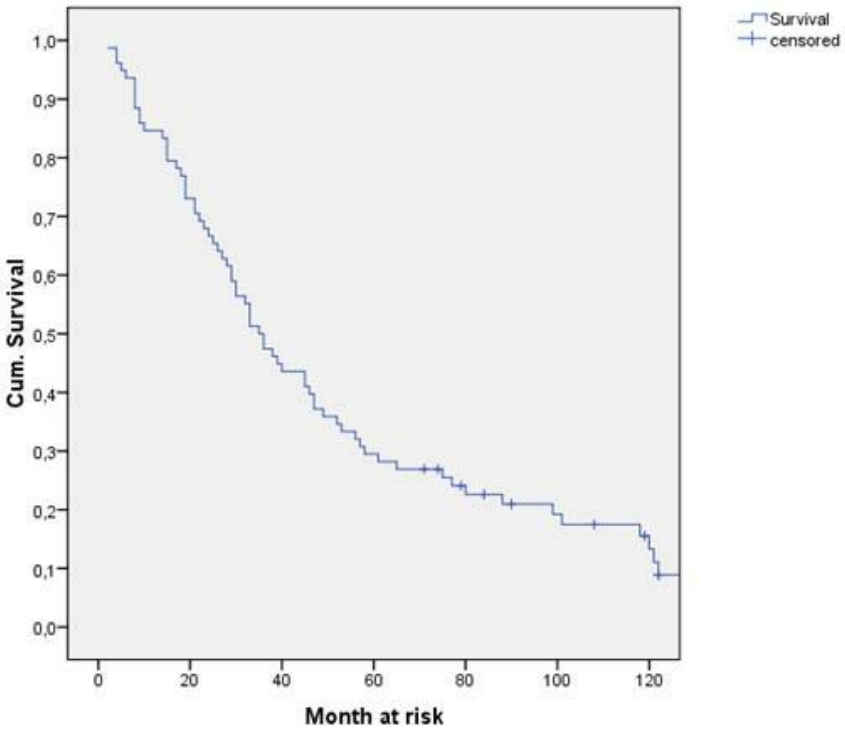
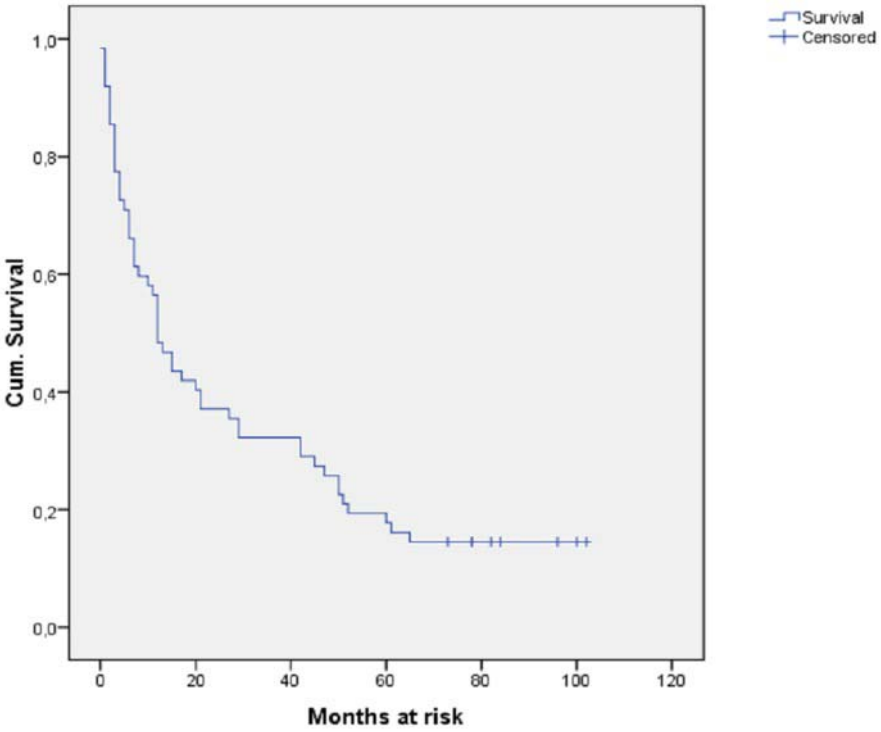

Survival
censored
Cum. Survival
1,0
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0,0
0
20
40
60
80
100
120
Month at risk

Figure 2


Survival
Censored
Cum. Survival
1,0
0,8
0,6
0,4
0,2
0,0
0
20
40
60
80
100
120
Months at risk