Clinical efficacy, safety, tolerability, and survival outcome of long-term inhaled iloprost treatment in the management of pulmonary arterial hypertension: Data from prospective multicenter observational OPTION study

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Abstract

Objective: To evaluate clinical efficacy, safety and tolerability of long-term inhaled iloprost treatment in the daily practice for the management of pulmonary arterial hypertension (PAH).

Methods: A total of 115 patients with PAH on inhaled iloprost treatment were included. New York Heart Association (NYHA) functional class, brain natriuretic peptide (BNP) and N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels, and 6-minute walk distance (6MWD) were recorded at baseline and at 3rd to 24th month visits. Safety and tolerability of iloprost treatment were also evaluated during follow-up, as were the survival, clinical worsening, and the related risk factors.

Results: The treatment was associated with an increase in the percentage NYHA functional class II (from 0.0% at enrolment to 36.2% at 24th month visit) patients but no significant difference was noted in 6MWD values. Clinical worsening was observed in 63.5% patients, while survival rate was 69.6%. NT-proBNP levels were significantly higher in non-survivors than in survivors (p=0.042). Cox regression analysis revealed the association of female sex [odds ratio (OR)=0.318; 95% confidence interval (CI), 0.128-0.792; p=0.014] and scleroderma-related PAH (OR=0.347; 95% CI, 0.140-0.860; p=0.022) with significantly lower risk (3.14 fold and 2.88 fold, respectively) of mortality.

Conclusion: Our findings indicate favorable efficacy, safety, and tolerability of long-term iloprost treatment in the management of PAH, whereas improved NYHA functional class was not accompanied with a significant change in 6MWD values. Patient age was a risk factor for clinical worsening, while female sex, scleroderma subtype, and lower NT-proBNP levels were associated with significantly lower mortality risk.

Keywords: pulmonary arterial hypertension, iloprost, treatment outcome, safety, survival

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Introduction

Pulmonary arterial hypertension (PAH) is a progressive and potentially fatal disease characterized by persistent vasoconstriction and remodeling of the resistance arterioles in pulmonary vasculature with increased pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR) leading to progressive right ventricular failure (RVF) and death (1-4).

The development of pathway-specific targeted drugs has considerably improved the management of PAH by symptom

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HIGHLIGHTS

- Efficacy, safety, and tolerability of inhaled iloprost therapy in pulmonary arterial hypertension (PAH) were evaluated.
- Long-term inhaled iloprost had favorable efficacy, safety, and tolerability profile.
- The New York Heart Association functional class was improved without a significant change in 6-minute walk distance values.
- Patient age was a risk factor for clinical worsening.
- Gender, PAH subtype, and N-terminal pro–B-type natriuretic peptide levels were associated with mortality risk.

reduction, deceleration of disease progression, and prolonged survival (5-7). Currently approved PAH-specific medicines address the three principal signaling pathways of pulmonary vasoregulation, including prostacyclin pathway (epoprostenol, iloprost, treprostinil, beraprost, and selexipag), nitric oxide pathway (sildenafil, tadalafil, vardenafil, and riociguat), and endothelin pathway (bosentan, ambrisentan, and macitentan) (2, 8).

Iloprost is an inhaled prostacyclin-based therapy for PAH with vasodilatory and anti-proliferative effects (9-11), enabling significant improvements in exercise capacity, symptoms, and PVR and lesser incidence of clinical events in patients with PAH than with placebo (2, 9, 12). Thus, inhaled iloprost is currently recommended as class I monotherapy for patients with PAH in New York Heart Association (NYHA) functional class III, as class IIb monotherapy for patients in NYHA functional class IV, and as class IIb sequential combination therapy (add on to bosentan) for those in NYHA functional class II to IV (2, 13, 14).

Inhaled iloprost has emerged as a major strategy in the treatment of PAH with certain advantages such as few systemic adverse effects, simple delivery, and vasodilation through different cellular mechanisms (15-17). However, its relatively short half-life necessitating frequent dosing (6-9 times per day) is considered likely to affect adherence (7), in addition to a paucity of clinical evidence regarding its therapeutic effectiveness in the long-term (15, 18).

This observational multicenter study was therefore designed to evaluate clinical efficacy, safety, and tolerability and survival outcome of long-term inhaled iloprost treatment in the management of PAH.

Methods

Study population

A total of 115 patients with PAH who were on inhaled iloprost treatment were included in this open-label, uncontrolled, multicenter, and non-interventional observational study with an enrolment period of February 2011 and February 2015 at 27 centers across Turkey. Adult (≥18 years old) patients diagnosed with NYHA Class III-IV (requiring an improved exercise capacity and symptom control) PAH (idiopathic, familial, or secondary to scleroderma in the absence of interstitial lung disease) and initiated on iloprost treatment before enrolment owing to the insufficiency of standard therapies were included in the study. Presence of severe coronary heart disease or unstable angina, myocardial infarction within the last six months, decompensated cardiac failure if not under close medical supervision, severe arrhythmias, suspected pulmonary congestion, cerebrovascular events (e.g. transient ischemic attack, stroke) occurred within last three months, pulmonary hypertension because of venous occlusive disease, congenital or acquired valvular defects with clinically relevant myocardial function disorders not related to PAH, and pregnancy or lactation were the exclusion criteria of the study.

Written informed consent was obtained from each patient following a detailed explanation of the objectives and protocol. The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and approved by the Institutional Ethics Committee.

Data collection

Data on patient demographics (age, gender), PAH characteristics (clinical subgroup, duration, symptoms, Borg dyspnea score), NYHA functional class, iloprost treatment (monotherapy, combination therapy, inhalation dosage and frequency), co-morbid diseases, concomitant treatments, vasoreactivity test, hemodynamic parameters, biomarker levels [brain natriuretic peptide (BNP), N-terminal pro–B-type natriuretic peptide (NT-proBNP)], and 6-minute walk distance (6MWD) were obtained at the time of enrolment. Patients were followed up for 24 months after enrolment. Safety [adverse events (AEs), serious AEs (SAEs)] and tolerability of iloprost treatment were also evaluated during follow-up as were the survivorship status, clinical worsening, and the related risk factors.

Clinical worsening over the follow-up period was assessed on the basis of the presence of at least any one or more of the following markers; clinically significant deterioration of 6MWD compared with reference baseline values, worsening according to NYHA functional class, change or addition of drug treatment for PAH, PAH-related hospitalization, heart and/or lung transplantation, and survivorship status.

Outcome measures

The primary outcome measure was the efficacy of inhaled iloprost treatment on the basis of change from baseline reference 6MWD values during follow-up visits. Secondary outcome measures were the change in NYHA functional class and biomarker levels during follow-up, rates and risk factors for clinical worsening and survival outcome, as well as safety and tolerability of inhaled iloprost treatment.

Consistent with non-interventional design, duration of iloprost treatment, and timing of follow-up visits were at physicians' discretion according to the local prescribing information and routine medical practices. If the patients deteriorated on

inhaled iloprost, the treating physician was free to initiate any alternative treatment, and the assessment of 6MWD was recommended before addition or change in therapy.

Six-minute walk test

The 6MWT was performed to determine 6MWD along with the degree of perceived exertion by means of Borg dyspnea scale (6-20 scale), both before and after the test (2, 19, 20). 6MWT is used to determine functional exercise capacity, assess treatment efficacy, predict prognosis, and establish rehabilitation programs in patients with PAH, whereas 6MWD has been specified as the main clinical outcome in PAH and has been used as the primary end-point in multiple studies conducted for new PAH treatments (2, 19, 21).

Statistical analysis

Although 160 patients were planned to be enrolled in the study according to the sample size calculation based on the standard deviation observed in the phase III study for patients with PAH NYHA functional class III (s observed, 67 m; s expected, <75 m), only 115 patients who were eligible according to inclusion/exclusion criteria were included in the study.

Statistical analysis was done using IBM Statistical Product and Service Solutions for Windows, version 22.0 (IBM Corporation, Armonk, NY, USA). Fisher's exact test was used for comparison of categorical data and Mann-Whitney U test for the comparison of non-normally distributed numerical variables. Change over time was analyzed via Wilcoxon signed rank test and repeated measures analysis of variance (ANOVA) with Bonferroni corrections. 6MWD analyses were based on constructing two one-sided hypotheses in the 95% confidence interval (CI). Survival analyses were analyzed using the Kaplan-Meier method. Cox regression analysis was used to identify the effect of risk factors on survival. For categorical variables, missing data of the patients were not included in calculations of percentages unless otherwise specified. Continuous data were expressed as mean±standard deviation and median (minimum-maximum), and categorical data were expressed percent. P<0.05 was considered statistically significant.

Results

Patient demographics and clinical characteristics at the enrolment (n=115)

Mean age of patients was 50.7 (range, 19.2-84) years, and women comprised 79.1% of the study population. Duration of disease was median 1.9 years, whereas the clinical PAH subgroup was idiopathic PAH in 74.8% of patients (Table 1).

Dyspnea (94.8%) was the most common symptom, followed by right heart failure symptoms (36.5%). Median (minimum-maximum) Borg dyspnea score was 11.5 (6.0-20.0). Co-morbid diseases were evident in 35.6% of patients and abnormal chest X-ray and electrocardiogram findings in 93.7% and 88.7% of patients, respectively (Table 1).

Table 1. Patient demographics and baseline clinical characteristics (n=115)

Patient demographics		
Age (year)	Mean±SD	50.7±15.9
	Median (min-max)	51.2 (19.2-84.0)
Gender, n (%)	Male	24 (20.9)
	Female	91 (79.1)
PAH clinical subgroup, n (%)		
Idiopathic PAH		86 (74.8)
PAH secondary to scleroderma		26 (22.6)
Familial PAH		3 (2.6)
PAH duration (year),	Mean±SD	3.0±5.0
	Median (min-max)	1.9 (0.0-42.5)
Hospitalization because of PAH within the last month, n (%)		20 (17.4)
PAH symptoms, n (%)[a]		110 (95.7)
Dyspnea		109 (94.8)
RHF symptoms (peripheral edema, jugular congestion, change of weight, ascites, and/or hepatic pulse)		42 (36.5)
Cyanosis		25 (21.7)
Coughing		21 (18.3)
Chest pain		11 (9.6)
Syncope		2 (1.7)
Borg dyspnea score, median (min-max)		11.5 (6.0-20.0)
Co-morbid diseases, n (%)		41 (35.6)
Hypertension		15 (13.0)
Type 2 diabetes		10 (8.7)
Abnormal chest X-ray findings		89 (93.7)
Pulmonary conus enlargement		79 (68.7)
Enlarged right heart silhouette		76 (66.1)
Enlarged pulmonary segment and vessels		74 (64.3)
Globally enlarged heart		63 (54.8)
Other		15 (13.0)
Abnormal ECG findings[b], n (%)		94 (88.7)
P pulmonale		50 (47.6)
ST depression		52 (49.0)
Right bundle branch block		50 (47.2)
Arrhythmia	Sinus	89 (84.7)
	NA	16 (15.3)
Axis	Right	57 (53.8)
	Left	5 (4.7)
Vasoreactivity test, n (%)[c]	Performed	95 (88.0)
	Positive	6 (6.4)

[a]Number of patients with at least one PAH symptom. Missing data for [b]nine patients and, [c]20 patients (performed with iloprost in 38 patients)
ECG - electrocardiogram; max - maximum; min - minimum; PAH - pulmonary arterial hypertension; RHF - right heart failure; SD - standard deviation

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Table 2. Characteristics of iloprost treatment and hemodynamic findings at study enrolment			
Iloprost therapy, n (%)		115 (100.0)	
Monotherapy		47 (40.9)	
Double combination		44 (38.2)	
Iloprost, bosentan		29 (25.2)	
Iloprost, sildenafil		15 (13.0)	
Triple combination		24 (20.9)	
Iloprost, sildenafil, bosentan		23 (20.0)	
Iloprost, sildenafil, ambrisentan		1 (0.9)	
	n	**Mean (SD)**	**Median (min-max)**
Iloprost aerosol dose (µg/inhalation)	114	11.9 (4.9)	10.0 (5.0-25.0)
Inhalation frequency	114	7.5 (1.6)	8.0 (2.0-9.0)
Night inhalation, n (%)	No	75 (66.4)	
	Rarely	15 (13.3)	
	Regularly	23 (20.3)	
Patient compliance with all doses, n (%)	No	2 (1.7)	
	Yes	112 (98.3)	
Hemodynamic catheter test findings	**n**	**Median (min-max)**	
LAP mean (mm Hg)	24	9.5 (6.0-55)	
LVO_2 (%)	8	82.0 (8.0-96.0)	
PAP mean (mm Hg)	107	49.0 (10.0-108.0)	
PAO_2 (%)	44	64.5 (34.0-89.0)	
RV mean (mm Hg)	38	30.0 (0.8-150.0)	
RAP mean (mm Hg)	43	12.0 (4.0-26.0)	
CO (L/min)	42	4.0 (2.2-10.0)	
PVR (dyne)	64	9.0 (0.6-49.0)	
CI (L/min/m^2)	31	2.1 (1.2-4.6)	
QP/QS	27	1.0 (1.0-5.0)	
SVR (dyne)	23	22.5 (9.5-54.0)	

CI - cardiac index; CO - cardiac output; LVO_2 - left ventricular oxygen saturation; PAH - pulmonary arterial hypertension; PAO_2 - pulmonary arterial oxygen saturation; PVR - pulmonary vascular resistance; QP/OS - pulmonary/systemic flow; RAP - right atrial pressure; RV - right ventricular systolic pressure; SD - standard deviation; SVR - systemic vascular resistance

Characteristics of iloprost treatment and hemodynamic findings at study enrolment

At study enrolment, iloprost treatment involved monotherapy in 40.9% of patients, double combination in 38.2% (with bosentan in 25.2% and sildenafil in 13.0%), and triple combination in 20.9% (with sildenafil and bosentan in 20.0% and with sildenafil and ambrisentan in 0.9%) of patients. Median aerosol dose was 10.0 (range, 5.0-25.0) µg/inhalation and median inhalation frequency was 8.0 (range, 2.0-9.0) times with no night inhalation in 66.4% of patients. Overall, 98.3% of patients were compliant with all doses (Table 2).

Hemodynamic catheter test findings at study enrolment are provided in Table 2.

Six-minute walk distance values at follow-up visits

Median 6MWD values measured at 3rd month, 6th month, 12th month, 18th month, and 24th month follow-up visits were 351 (47-817), 360 (26-780), 360 (26-780), 372 (140-760), and 358 (60-750) m, respectively (Table 3).

No significant difference was noted between 6MWD values or change from baseline at follow-up visits (Table 3).

NYHA functional class and biomarkers at follow-up visits

During follow-up, an increase in the percentage of patients in NYHA functional class II (from 0.0% at enrolment to 36.2% at 24th month visit) was noted along with a decrease in the percentage of patients in NYHA functional class III (from 87.8% at enrolment to 51.7% at 24th month). Worsening in NYHA functional class was noted in 2.9% (3rd month) and 3.4% (24th month) of patients when compared with baseline status, and in 13.0% (24th month) of patients when compared with previous visit status (Table 3).

Median (minimum-maximum) levels for BNP and NT-proBNP were 376.1 (2.0-20016) and 875 (24-7385) pg/mL at baseline, re-

Table 3. Six-minute walk distance, NYHA class, and biomarkers during study visits

6MWD visit values (m)	**n**	**Median (min-max)**				
At enrolment (baseline)	101	320 (49-680)				
3rd month visit	90	351 (47-817)				
6th month visit	89	360 (26-780)				
12th month visit	62	360 (26-780)				
18th month visit	50	372 (140-760)				
24th month visit	42	358 (60-750)				
P-value[1]	0.058					
6MWD-change from baseline (m)	**n**	**Median (min-max)**	***P*-value[2]**			
3rd month visit	83	-14 (-237-350)	0.028			
6th month visit	82	-10 (-270-352)	0.062			
12th month visit	56	-35.5 (-180-210)	0.07			
18th month visit	56	-15 (-226-296)	0.247			
24th month visit	24	-20 (-175-230)	0.166			
P-value[1]	0.052					
NYHA functional class, n (%)	**Baseline (n=115)**	**3rd month (n=103)**	**24th month (n=58)**			
Class I	0	0	0			
Class II	0	32 (31.1)	21 (36.2)			
Class III	101 (87.8)	60 (58.2)	30 (51.7)			
Class IV	14(12.2)	11 (10.7)	7 (12.1)			
NYHA worsening, n (%)	**Baseline (n=115)**	**3rd month (n=103)**	**24th month (n=58)**			
From baseline	Class II to III	—	—			
	Class III to IV	3 (2.9)	4 (3.4)			
From the previous visit	Class II to III	—	6 (11.1)			
	Class III to IV	—	1 (1.9)			
Biomarker levels[3]	**Baseline (n=115)**		**3rd month (n=103)**		**24th month (n=58)**	
	n	**median (min-max)**	**n**	**median (min-max)**	**n**	**median (min-max)**
BNP (pg/mL)	27	376.1 (29-20016)	17	389 (54-15783)	4	1044.1 (78-1994)
NT-proBNP (pg/mL)	29	875 (24-7385)	23	866 (21-8299)	10	858.6 (117-2614)

[1]Friedman test; [2]Repeated measures ANOVA with Bonferroni corrections (*P*<0.01); [3]No significant change (Wilcoxon signed rank test)
6MWD - 6-minute walk distance; BNP - B-type natriuretic peptide; max - maximum; min - minimum; NYHA - New York Heart Association; NT-proBNP - N-terminal pro–B-type natriuretic peptide

spectively, with no significant change from baseline levels at follow-up visits (Table 3).

Treatment regimens during follow-up

At 3rd, 6th, 12th, 18th, and 24th month visits, patients were treated with monotherapy in 35.0%, 31.0%, 29.1%, 28.6%, and 24.6% of patients; as double combination in 41.7%, 45.0%, 48.1%, 41.3%, and 49.1% of patients; and as triple combination in 22.3%, 24.0%, 22.8%, 30.2%, and 26.3% of patients, respectively (Fig. 1).

Risk factors for clinical worsening and mortality

Overall, clinical worsening was observed in 73 (63.5%) patients within median 12.0 months (95% CI, 6.9-17.2), and the survival time was 43 months and the survival rate was 69.6% with mortality in 35 (30.4%) patients (Table 4, Fig. 2).

Patient age was significantly higher for those with than without clinical worsening (mean±SD, 53.4±14.2 vs. 46.6±17.4 years, p=0.041), and NT-proBNP levels were significantly higher in non-survivors than in survivors [median (minimum-maximum), 1291 (24-10848) vs. 622 (14-5778) pg/mL, p=0.042], whereas other parameters had no significant impact on clinical worsening or mortality (Table 4).

Cox regression analysis for risk factors of mortality

Cox regression analysis revealed the association of female sex (OR=0.318; 95% CI, 0.128-0.792; p=0.014) and scleroderma-related PAH (OR=0.347; 95% CI, 0.140-0.860; p=0.022) with signifi-

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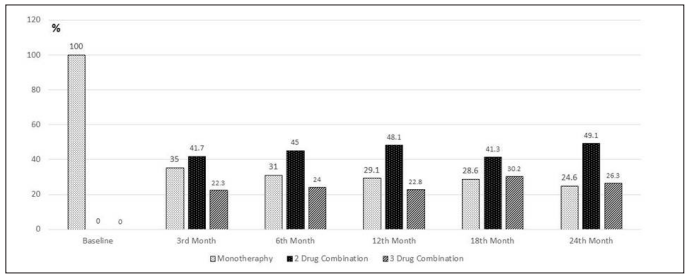

Figure 1. Iloprost-based treatment regimens during follow-up

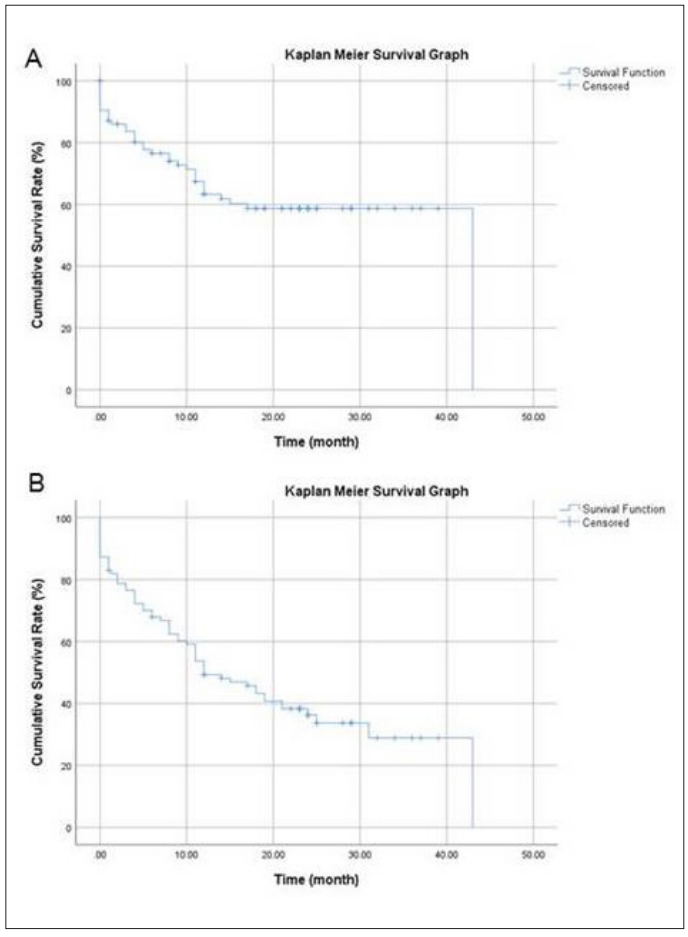

Figure 2. Kaplan-Meier analysis for, a) survival time (month) and, b) clinical worsening time (month) as calculated according to hospitalization, death, transplantation, and worsening in walking distance test

cantly lower risk (3.14 fold and 2.88 fold, respectively) of mortality. Age and NYHA functional class variables had no significant impact on risk of mortality (Table 5).

No significant difference was noted in mean (SE, 95%CI) survival time with respect to age groups [<30 years: 33.8 (2.9, 28.2-39.5) months, 30 to 49 years: 31.2 (3.1, 25.1-37.4) months, 49.1 to 64 years: 19.5 (2.0, 15.5-23.5) months, 64.1 to 74 years: 22.6 (2.3, 18.2-27.1) months, Log rank p value 0.349].

Safety data

Overall, a total of 29 AEs were reported and the most frequently observed AEs were dyspnea (27.6%), cyanosis (13.8%), and cough (13.8%). There were 124 SAEs and the most frequently reported SAEs were RVF (13.7%), dyspnea (9.7%), respiratory failure (8.9%), and pneumonia (8.9%) (Table 6).

There were 35 deaths (30.2%) reported in this study, none of which was considered related to the treatment (causality not reported in one patient). The most frequent reason for death was AEs (62.1%), which was related to the primary diagnosis of the patients, resulting in cardiovascular deterioration and consequent mortality.

Discussion

Our findings revealed improved NYHA functional class status, which was not accompanied with significant improvement in 6MWD from enrolment to 24th month visit in patients with PAH under iloprost treatment. Clinical worsening was noted in 63.5% of patients within a median 12-month of therapy, whereas survival rate was 69.6%. Clinical worsening was more likely in older patients, and NT-proBNP levels were significantly higher in non-survivors than in survivors. Female gender and scleroderma-related PAH were determined to be associated with significantly lower mortality risk; however, neither age nor NYHA functional class had a significant impact on mortality risk.

During the study period, the rate of iloprost monotherapy decreased (from 40.9% at enrolment to 24.6% at 24th month visit) alongside an increase in the rate of double (from 38.2% to 49.1%) and triple (from 20.9% to 26.3%) combinations. This seems consistent with the widespread use of sequential combination therapy in current clinical practice worldwide as recommended by the international guidelines for PAH treatment (2, 15, 22).

Accordingly, our findings support the data from previous clinical trials on safety and efficacy of iloprost aerosol therapy in NYHA functional class III or IV patients with PAH either in monotherapy or in combination with other specific drugs targeting endothelin and nitric oxide pathways (9, 10, 15, 23-26). Notably, data from a recent meta-analysis of 10 studies in a total of 370 patients treated with inhaled iloprost indicated that it is associated with a significant improvement in 6MWD in the short-medium and prolonged treatment groups, as well as with the improved functionality by at least one class in 48.7% of patients (23).

Albeit a tendency for a considerable increase was noted in 6MWD values from baseline within the first three months of therapy (from median 320 m to 350 m), our findings revealed no significant difference between 6MWD values or change from baseline recorded at follow-up visits. In a meta-analysis included six datasets of PAH therapies with random controlled trials (RCT) and corresponding open-label extension studies, baseline 6MWDs were reported to range from a mean of 330 to 368 m and considered to be reflective of a patient population in predominantly WHO functional class III (27). Authors indicated the overall fixed-effects estimate of mean difference in change in 6MWD from pivotal RCT baseline and from baseline before first active dose to be 14.6 m (95% CI, 5.6-23.5) and 20.5 m (95% CI, 10.4-30.7), respectively (27). However, in a meta-analysis of 22 RCTs assessing 6MWD in patients with PAH, changes in 6MWD were concluded not to reflect benefit in clinical outcomes related to

Table 4. Risk factors for clinical worsening and mortality

		Clinical worsening			Survivorship status		
Risk factors		**Absent (n=42)**	**Present (n=73)**	***P*-value**	**Survivor (n=80)**	**Non-survivor (n=35)**	***P*-value**
Age (years)	Mean (SD)	46.6±17.4	53.4±14.2	0.041[1]	49.4±16.7	53.7±13.8	0.158[1]
	Median (min-max)	48.6 (19.2-75.0)	51.7 (20.9-84.06)		49.0 (19.2-79.0)	49.0 (22.5-84.1)	
Gender, n (%)	Female	32 (76.2)	59 (80.8)	0.556[2]	14 (17.5)	10 (28.6)	0.125[4]
	Male	10 (23.8)	14 (19.2)		69 (82.5)	25 (71.4)	
BNP (ng/L)	Median (min-max)	322.5 (48-20016)	348.0 (12-7042)	0.985[1]	203.1(12-2001.6)	546 (82-2125)	0.175[1]
NT-proBNP (ng/L)	Median (min-max)	821.9 (14-5778)	551.0 (24-10848)	0.694[1]	622 (14-5778)	1291 (24-10848)	0.042[1]
PAH subgroup, n (%)	Familial	0	3 (4.1)	0.182[3]	2 (2.5)	1 (2.9)	0.053[3]
	Idiopathic	35 (83.3)	51 (69.9)		665 (81.3)	21 (60)	
	Scleroderma	7 (16.7)	19 (26)		13 (16.3)	13 (37.1)	
NYHA functional class, n (%)	Class III	N/A*			69 (86.2)	32 (91.4)	0.546[4]
	Class IV				11 (13.8)	3 (8.6)	

[1]Mann-Whitney U test; [2]Continuity correction; [3]Chi-square test; [4]Fisher's exact test; NC: No statistical comparison could be performed due to low number of patients in subgroups; *Not included in the analysis for clinical worsening, since NYHA functional class is a parameter already included in clinical worsening assessment
BNP - B-type natriuretic peptide; max - maximum; min - minimum; N/A - not available; NT-Pro BNP - N-terminal pro–B-type natriuretic peptide; NYHA - New York Heart Association, PAH - pulmonary arterial hypertension; SD - standard deviation

Table 5. Cox regression analysis for risk factors of mortality

							95.0% CI for Exp (B)	
	B	**SE**	**Wald**	**Df**	**Sig.**	**Exp (B)**	**LB**	**UB**
Risk factors								
Age	0.014	0.013	1.130	1	0.288	1.014	0.989	1.040
Gender (Female)	-1.146	0.466	6.056	1	0.014	0.318	0.128	0.792
PAH subgroup			6.329	2	0.042			
PAH subgroup (idiopathic)	-0.004	1.179	0.000	1	0.998	0.996	0.099	10.045
PAH subgroup (scleroderma)	-1.058	0.463	5.219	1	0.022	0.347	0.140	0.860
NYHA functional class	-0.583	0.617	0.892	1	0.345	0.558	0.167	1.871

CI - confidence interval; df – degrees of freedom; Exp (B) - exponentiation of the B coefficient; LB - lower bound; NYHA - New York Heart Association; PAH - pulmonary arterial hypertension; SE - standard error; UB - upper bound; Sig. - significance

Anatol J Cardiol 2021; 25: 721-32
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Table 6. Safety data		
Non-serious adverse events		**n (%)**
Total		**29 (100.0)**
By system organ class		
Blood and lymphatic system disorders	Iron deficiency anemia	1 (3.5)
	Leukocytosis	1 (3.5)
Cardiac disorders	Atrial fibrillation	1 (3.5)
	Bradycardia	1 (3.5)
	Cyanosis	4 (13.8)
	Palpitations	1 (3.5)
General disorders and administration site conditions	Edema peripheral	1 (3.5)
Investigations	Weight decreased	1 (3.5)
Nervous system disorders	Headache	1 (3.5)
	Loss of consciousness	1 (3.5)
Respiratory, thoracic and mediastinal disorders	Cough	4 (13.8)
	Dyspnea	8 (27.6)
	Pulmonary hypertension	2 (6.9)
Skin and subcutaneous tissue disorders	Night sweats	1 (3.5)
Vascular disorders	Jugular vein distension	1 (3.5)
Serious adverse events		**n (%)**
Total		**124 (100.0)**
By system organ class		
Blood and lymphatic system disorders	Anemia	1 (0.81)
Cardiac disorders	Angina pectoris	1 (0.8)
	Cardiac arrest	4 (3.2)
	Cardiac failure	3 (2.4)
	Cardiac failure congestive	1 (0.8)
	Cardiovascular disorder	3 (2.4)
	Cardiovascular insufficiency	1 (0.8)
	Cor pulmonale	2 (1.6)
	Coronary artery insufficiency	1 (0.8)
	Cyanosis	1 (0.8)
	Myocardial infarction	2 (1.6)
	Palpitations	1 (0.8)
	Right ventricular failure	17 (13.7)
General disorders and administration site conditions	Condition aggravated	1 (0.8)
	Death	3 (2.4)
	Disease progression	1 (0.8)
	Fatigue	1 (0.8)
	Multiple organ dysfunction syndrome	1 (0.8)
	Edema	2 (1.6)
	Edema peripheral	1 (0.8)

Table 6. Safety data (continued)		
Infections and infestations	Bronchitis	1 (0.8)
	Kidney infection	1 (0.8)
	Pneumococcal sepsis	1 (0.8)
	Pneumonia	11 (8.9)
	Sepsis	1 (0.8)
Investigations	Intracardiac pressure increased	1 (0.8)
	Catheterization cardiac	1 (0.8)
	International normalized ratio increased	1 (0.8)
	Hemoglobin decreased	1 (0.8)
Musculoskeletal and connective tissue disorders	Fistula	1 (0.8)
	Myalgia	1 (0.8)
Neoplasms benign, malignant and unspecified (cysts and polyps)	Myelodysplastic syndrome	1 (0.8)
	POEMS syndrome	1 (0.8)
Nervous system disorders	Syncope	4 (3.2)
Renal and urinary disorders	Acute kidney injury	2 (1.6)
Respiratory, thoracic and mediastinal disorders	Acute respiratory failure	1 (0.8)
	Cough	2 (1.6)
	Dyspnea	12 (9.7)
	Hemoptysis	2 (1.6)
	Interstitial lung disease	1 (0.8)
	Pulmonary arterial hypertension	7 (5.7)
	Pulmonary hypertension	8 (6.5)
	Respiratory acidosis	1 (0.8)
	Respiratory arrest	1 (0.8)
	Respiratory failure	11 (8.9)
Surgical and medical procedures	Lung transplant	1 (0.8)

POEMS - polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes

NYHA functional class and Borg dyspnea score, or time to clinical worsening or clinical event occurrence (28). In fact, threshold values of 6MWD, rather than changes induced by therapies have been suggested to be prognostic predictors, with increased risk of mortality in patients with 6MWD of <250 m and substantially lower mortality in patients with 6MWD ≥440 m (29, 30).

Long-term, open-label studies have also supported the clinical benefit of continued iloprost therapy in patients with PAH (27-30), including sustained effects on exercise capacity and pulmonary hemodynamics with excellent tolerability over 12 months (31), improved survival (87%) and favorable tolerability over a period of two years (32), improved WHO functional class, 6MWD and systemic arterial oxygen saturation over 48 weeks (33), and persistence with treatment (78%) and lack of clinical worsening (81%) over one year (34). Two-year survival rate was reported to be 87% among 40 patients with idiopathic PAH (33); although in a cohort of 267 patients with PAH treated with iloprost, a three-year survival rate was reported to be 54% despite significant improvements in physical (6MWT) and functional (WHO functional class) performance, which has been linked to use of the drug in high-risk patients with discontinuation rate as high as 75% (15).

Survival rate was 69.6% in the present cohort of patients with PAH who were treated with iloprost before to enrolment and continued therapy after the enrolment with increasing rates for combination over monotherapy. This seems consistent with the estimated three-month, six-month, one-year, and two-year event-free survival rates of 96.6%, 92.3%, 62.6%, and 39.6%, respectively, reported in a recent meta-analysis of 10 studies in 370 patients with PAH treated with iloprost, authors of which also emphasized a potential risk of an unsatisfactory improvement in vascular remodeling and even a decreased event-free survival rate with the use of inhaled iloprost monotherapy for a prolonged period beyond the first three months after diagnosis (23).

The median survival time of 43 months also seems consistent with the high prevalence of idiopathic PAH (74.8%) in our cohort

Anatol J Cardiol 2021; 25: 721-32
DOI:10.5152/AnatolJCardiol.2021.03009

given its association with only 2.8±0.9 years of mean survival time reported in the past studies (35, 36). Our findings indicated that scleroderma-related PAH was associated with 2.88-fold reduction in the risk of mortality. In addition, female sex was also associated with 3.14-fold reduction in the risk of mortality in the current study. Given the female predominance in our cohort of patients, supporting the higher prevalence of PAH among women reported in epidemiological studies, it should also be noted that male patients with PAH are considered to be affected by higher degree of right ventricular dysfunction leading to poorer outcome, alongside the better treatment results with prostacyclin analogues and endothelin receptor antagonists in female patients with PAH (37).

In a recent Bayesian network meta-analysis of 10,230 patients from 45 qualified trials on the efficacy and safety of 18 targeted drugs or drug combinations for PAH, the combination of iloprost and bosentan was determined to perform best for lowering mean pulmonary arterial pressure (mPAP) and PVR and decreasing the incidence of clinical worsening; whereas vardenafil was considered superior to other medications in terms of low withdrawal rate and improved Borg dyspnea score; and ambrisentan plus tadalafil was considered superior in terms of efficacy on 6MWD and the occurrence of hospitalization (38). Notably, although no single therapy was concluded to be outstanding in the majority of investigated endpoints, vardenafil and iloprost+bosentan were considered to be the medications associated with a better performance in terms of both efficacy and safety (38).

Circulating levels of natriuretic peptides has been considered useful in detection of PAH or as indicators of a therapeutic response, being associated with hemodynamics and survival in patients with PAH (39, 40). In the phase three, double-blind Double Blind Placebo Controlled Clinical Investigation Into the Efficacy and Tolerability of Inhaled Treprostinil Sodium in Patients With Severe Pulmonary Arterial Hypertension (TRIUMPH) trial, significant difference was reported between PAH-related targeted therapies (inhaled treprostinil on background therapy with bosentan or sildenafil) vs. placebo in terms of median change in NT-proBNP (41). In addition, significantly greater decrease in NT-proBNP for combination vs. monotherapy was reported in phase 3/4, double-blind The Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension (AMBITION) trial (ambrisentan plus tadalafil vs. ambrisentan or tadalafil) (42) and in phase four, open-label ATHENA-1 trial (ambrisentan plus PDE5i vs. PDE5i) (43).

Our findings revealed no significant change from baseline BNP and NT-proBNP levels during follow-up visits and no impact of BNP on clinical worsening or survival, whereas significantly higher NT-proBNP levels were noted in survivors vs. non-survivors. Notably, NT-proBNP was reported to be associated with NYHA functional class, 6MWD, and survival in patients with PAH, and increased mortality risk with every 10-fold increase in NT-proBNP both at baseline [hazards ratio (HR), 4.82] and at follow-up (HR, 3.82) (44) and higher survival with >15% decrease per year (45). Hence, our findings support the predictive value of NT-proBNP levels for mortality and likelihood of change over time in NT-proBNP to be more relevant than a target value in assessing response to therapy (40, 45).

The adverse event (dyspnea in 27.6%, cough or cyanosis in 13.8%) and serious adverse event (right ventricular failure in 13.7%, dyspnea in 9.7%, respiratory failure or pneumonia in 8.9%) profile of iloprost in our cohort support the safety and tolerability consistent with typical prostanoid side effects reported in past studies indicating a tendency to increased coughing and flushing and high prevalence of adverse events over two-year treatment period with right heart failure as the most frequent serious adverse event (9, 32).

Study limitations

Certain limitations of this study should be considered. First, owing to its observational nature, non-randomized allocation and thereby the likelihood of main selection bias and confounding is possible. Second, although the data provided was through real-life clinical practice via multicenter design at 27 centers across Turkey, a potential lack of generalizability seems another important limitation because of the relatively small sample size. Third, missing data on certain variables and the discrepancy in improvement assessed via functional capacity and 6MWD outcome were other limitations owing to the non-interventional design, precluding the possibility of drawing verifiable and generalizable scientific conclusions. Fourth, the presence of both monotherapy and combination regimens was an important limitation, which jeopardizes the concrete efficacy outcome interpretation. Nonetheless, observational studies provide important information on pre-defined cohorts of patients who represent a certain population with similar disease characteristics with primary goals of describing patient profile and clinical status and assessing treatment outcomes.

Conclusion

Our findings indicate favorable efficacy, safety, and tolerability profile of long-term iloprost treatment in monotherapy or in combination among patients with PAH, whereas improved NYHA functional class was not accompanied with improved 6MWD values. Clinical worsening was noted in 53.9% of patients within a median 12-month of therapy, and survival rate was 69.6%. Our findings indicate that patients' age was a risk factor for clinical worsening; whereas female sex, scleroderma subtype, and lower NT-proBNP levels were associated with significantly lower mortality risk with no significant impact of age, BNP levels, and NYHA functional class on mortality risk. Further long-term large scale studies are warranted to elucidate the mechanisms of functional and physical activity changes induced by specific targeted therapies in PAH patients and their potential value in addition to natriuretic peptides as markers of disease progression or treatment outcome.

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