Impact of targeted pulmonary arterial hypertension therapies in severe pulmonary hypertension in chronic lung diseases

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Pulmonary arterial hypertension targeted therapies do not improve exercise capacity on 6MWD in severe group 3 pulmonary hypertension but could improve haemodynamic parameters
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Abstract

Research questions Patients with severe pulmonary hypertension associated with chronic lung disease have a poor prognosis. Targeted pulmonary arterial hypertension therapies might improve exercise capacity and outcome, but there are no guidelines on treatments which are not recommended because of an unproven benefit, with discordant results from few studies in this context. The aim of our study was to evaluate targeted pulmonary arterial hypertension therapies for severe group 3 pulmonary hypertension patients.

Study design and methods We conducted an observational retrospective monocentre study on patients with severe group 3 pulmonary hypertension diagnosed on right heart catheterisation treated with targeted therapies. Primary outcome was an improvement of the distance on 6-min walk test of ⩾30 m. Secondary end-points included changes in haemodynamics (pulmonary vascular resistance (PVR) and mean pulmonary arterial pressure (mPAP)) and identification of potential predictive factors of therapeutic response.

Results 139 patients were enrolled. Most patients had monotherapy with phosphodiesterase 5 inhibitors (n=128; 92%). Mean change in 6-min walk distance was +1.5 m after treatment (p=0.59). Forced expiratory volume in 1 s and forced vital capacity were not predictive factors for response. We found a significant improvement of PVR and mPAP of −1.0 Wood Units (p<0.001) and −4 mmHg (p<0.001), respectively, under treatment. 18% of patients had to withdraw treatment for intolerance. Treatment duration <3 months was associated with poor survival (hazard ratio 2.75, p=0.0005).

Conclusion Oral targeted pulmonary arterial hypertension therapies do not improve exercise capacity in patients with severe pulmonary hypertension associated with chronic lung disease, but could improve haemodynamic parameters.

Introduction

Pulmonary hypertension (PH) is a disease characterised by pulmonary vascular remodelling leading to right ventricular dysfunction. Depending on the mechanism involved, PH is classified into five groups [1]. Group 3 is secondary to chronic lung disease (CLD) and/or hypoxia, mostly COPD and interstitial lung disease (ILD) [2]. For these patients, PH represents an independent risk factor for mortality [3–6], is associated with an increased risk of exacerbations [6, 7] and impairs exercise capacity [8, 9].

Reviews [2, 10] have proposed to define severe PH in CLD with mean pulmonary arterial pressure (mPAP) ⩾35 mmHg or between 25 and 35 mmHg with a low cardiac index (<2.0 $L \cdot min^{-1} \cdot m^{-2}$),

associated with low pulmonary capillary wedge pressure (PCWP) ⩽15 mmHg. It has been shown that phenotypes in severe group 3 PH patients are different from those in mild to moderate ones. In COPD, the National Emphysema Treatment Trial registry reported that 38% of patients have mild-to-moderate PH, whereas only 1% will develop severe PH. Cardiopulmonary exercise testing in severe COPD-PH patients showed a cardiac limitation at the peak of exercise, which is unusual in advanced CLD and implies that different mechanisms are involved for these patients [11].

No pulmonary arterial hypertension (PAH)-targeted therapies are approved currently for group 3 PH patients. International guidelines suggest exclusively treating the underlying diseases [1]. A few studies have evaluated the efficacy of PAH-targeted therapies for group 3 PH patients, with a heterogeneous population, including patients with mild, moderate or severe CLD-PH, leading to contradictory results [12–17]. Limited data are available with PAH-targeted therapies in CLD-PH patients. The most frequently used therapy was phosphodiesterase 5 inhibitors (PDE5i) [18–21].

According to current guidelines [1], only severe CLD-PH should be assessed for individual-based treatments, but most studies have tried to evaluate PAH-targeted therapy independently of the severity of the disease [12–16]. In addition, diagnostic methods were not similar in all clinical trials, including the use of transthoracic echocardiography, while the gold standard is right heart catheterisation (RHC) [22–25]. Therefore, there is a lack of clear evidence of the benefit of PAH-targeted therapies in severe CLD-PH.

The aim of this study was to evaluate the efficacy and safety of such therapies in severe group 3 PH patients.

Methods

We conducted a retrospective, observational, monocentric study on adult patients treated for severe group 3 PH in the respiratory diseases department of Hôpital Nord (Marseille, France), from April 2014 to June 2021.

Patients included had severe group 3 PH defined by 1) mPAP ⩾35 mmHg or 2) 25–35 mmHg with low cardiac index (<2.0 $L \cdot min^{-1} \cdot m^{-2}$) on RHC before any treatment, and were all treated with targeted PAH therapy (PDE5i, endothelin receptor antagonist, soluble guanylate cyclase stimulator or prostanoids). Inclusion criteria were chosen according to current recommendations during development of the study and data collection.

Data were collected from patients' medical records. Clinical parameters analysed were functional class (FC) of dyspnoea based on New York Heart Association (NYHA) classification (from I to IV), resting oxygen requirement (oxygen blood pressure >60 mmHg) and 6-min walk distance (6MWD) performed under the supervision and guidance of experienced physiotherapists. This test was conducted on a 30-m track according to international guidelines [26]. It was performed with usual oxygen flow supplementation at exercise. Biological assessment includes N-terminal pro-brain natriuretic peptide (NT-proBNP) or BNP ($pg \cdot mL^{-1}$). Pulmonary function tests were done by the respiratory physiology team using European Respiratory Society standards [27]. Forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), total lung capacity (TLC) and diffusing capacity of the lung for carbon monoxide (D_{LCO}) were collected. RHC was performed by a team of experienced cardiologists from our centre for the measurement of mPAP, PCWP, cardiac output, cardiac index and pulmonary vascular resistance (PVR). Cardiac output and cardiac index were estimated using a thermodilution technique.

As recommended by international guidelines [1], patients were reassessed ⩾3 months after initiation of treatment with NYHA FC, 6MWD, biological tests, pulmonary function tests and RHC.

In previous studies, the primary end-point was change over time in 6MWD (minimal important difference 30 m retained as significant) from baseline to 3 months [12, 28, 29]. Secondary end-points were change in haemodynamic parameters (PVR, mPAP, cardiac output and cardiac index), functional parameters (FEV_1, FVC and D_{LCO}) and biological assays (BNP and NT-proBNP) from baseline to 3 months. In addition, we tried to define predictive factors of positive response for our primary end-point. Factors analysed were age, sex, type of CLD, NYHA FC, baseline BNP or NT-proBNP, baseline PVR, baseline cardiac index, baseline mPAP, baseline FEV_1, baseline FVC and type of treatment used. To homogenise the population, subgroup analyses with obstructive lung disease and ILD were performed. The entire population studied was followed until June 2021 (re-evaluation at 3 months of the last patient included in the study), and serious events were recorded throughout the study period.

First, a descriptive analysis was conducted. Quantitative variables were presented as mean±SD and categorical variables were presented as n (%). The efficacy of oral targeted PAH therapies was then

assessed by the estimation of the change in various parameters (haemodynamics, pulmonary function tests, biology, oxygen supplementation) between before treatment values and re-evaluation at 3 months values. Wilcoxon tests for paired data were used to compare these values. Univariate analyses were then conducted to identify potential determinants of response (30 m improvement in 6MWD from baseline). The Mann–Whitney test was used for quantitative potential determinants. The Chi-squared test (if valid; Fisher's exact test otherwise) was used for categorical potential determinants. Univariate Firth's bias-reduced penalised-likelihood logistic regression was performed to quantify the association between these potential determinants and the probability of response. Odds ratios were estimated with their 95% confidence intervals. Survival rates with 95% confidence intervals were estimated using the Kaplan–Meier method. Univariate Firth's bias-reduced penalised-likelihood Cox regression was performed to quantify the association between these potential determinants and the risk of death over time. Hazard ratios were estimated with their 95% confidence intervals. Tolerance was described by the rate of patients who presented at least one adverse event. Cumulative incidence of discontinuation of PH-targeted therapy over the first year of treatment was estimated using a time-to-event approach, taking into account the occurrence of death as a competing event. Univariate Fine–Gray regression was performed to quantify the association between potential determinants and the risk of therapy discontinuation over the first year of treatment. Subdistribution hazard ratios were estimated with their 95% confidence intervals. All analyses were realised using R (version 4.1.1). All tests were two-sided. $p<0.05$ was considered as statistically significant.

The study was validated by the institutional review board of the French Learned Society for Respiratory Medicine (Société de Pneumologie de Langue Française; CEPRO 2022-011), as well as by the data protection officer of our centre.

Results

Characteristics at inclusion

From April 2014 to June 2021, 262 patients were assessed for group 3 PH in our centre (fulfilling criteria of CLD-PH). Of these patients, 123 were excluded from the study (54 were not treated with targeted PAH therapy, 40 had mild-to-moderate PH and 29 could not be included because of a lack of data). Finally, a total of 139 patients with severe group 3 PH treated with targeted PAH therapy were included in the study.

In our study cohort, 69 patients had an obstructive lung disease, including 58 (85%) with COPD, three (4%) with cystic fibrosis, seven (10%) with noncystic fibrosis bronchiectasis and one (1%) with bronchopulmonary dysplasia. The other 70 patients had ILD, including 14 (20%) cases of systemic sclerosis, 11 (16%) cases of idiopathic pulmonary fibrosis (IPF), 11 (16%) cases of idiopathic nonspecific interstitial pneumonia, 11 (16%) cases of combined pulmonary fibrosis and emphysema and 23 (32%) patients had other ILD.

Mean FEV_1 was 48% predicted, mean FVC was 59% pred, mean TLC was 92% pred and mean D_{LCO} was 24% pred. In obstructive lung disease patients, mean FEV_1 was 32% pred and TLC was 117% pred. In the ILD population, mean FVC was 64% pred and mean TLC was 64% pred. At baseline, mean 6MWD was 310 m. 105 (75.5%) patients were treated with long-term oxygen therapy (LTOT).

Concerning haemodynamics, mean mPAP was 44 mmHg and mean PVR was 6.9 Wood Units. 137 (99%) patients were treated with a single PAH-targeted therapy and two (1%) patients were treated with a combination of two drugs. No patient received a triple therapy in our cohort. Patients were receiving PAH-targeted therapy at inclusion, mainly PDE5i (n=128, 92% including sildenafil (n=80) and tadalafil (n=48). 11 (8%) patients were treated with the endothelin receptor antagonist bosentan, whereas riociguat was used in two (1%) patients because of chronic thromboembolic pulmonary hypertension associated with CLD. The mean reassessment time was 150 days in the overall population.

The baseline characteristics of patients are summarised in table 1.

Follow-up at 3 months

Data on 6MWD were available for 77 patients. In our population, mean 6MWD change from baseline to 3 months was not statistically significant (+1.5 m at re-evaluation, p=0.59) (table 2). 35% of the patients were responders and presented a clinically significant improvement of ⩾30 m.

In the overall cohort, mean PVR and mean mPAP significantly decreased from baseline by −1.0 Wood Units ($p<0.001$) and −4 mmHg ($p<0.001$), respectively (table 2). These results were also found in the obstructive lung disease and ILD groups (table 2).

TABLE 1 Patient characteristics at baseline

	Patients	Overall population	Patients with OLD-PH	Patients with ILD-PH
Patients		139	69	70
Sex	139			
Male		86 (62)	39 (57)	47 (67)
Female		53 (38)	30 (43)	23 (33)
Age (years)	139	61.9±10.5	59±10	64.7±10
BMI (kg·m^{-2})	139	25.9±6.3	24.4±6.6	27.4±5.5
Aetiology	139			
OLD		69 (50)	69 (100)	0 (0)
ILD		70 (50)	0 (0)	70 (100)
NYHA FC	118			
I–II		15 (13)	7 (12)	8 (14)
III–IV		103 (87)	53 (88)	50 (86)
Oxygen supplementation (L·min^{-1})	138	2±1	2±2	3±2
6MWD (m)	107	310±124	303±122	317±127
Pulmonary function tests (% pred)				
FEV_1	131	48±26	32±19	65±23
FVC	132	59±23	55±22	64±24
TLC	128	92±36	117±30	64±20
D_{LCO}	67	24±13	24±17	24±10
NT-proBNP (pg·mL^{-1})	72	1023±2004	437±920	1547±2520
BNP (pg·mL^{-1})	62	102±139	60±67	150±180
Haemodynamic parameters				
mPAP (mmHg)	139	44±8	43±9	45±8
PVR (Wood Units)	136	6.9±3.2	6.7±3.3	7.1±3.1
Cardiac output (L·min^{-1})	137	5.0±1.4	5±1.3	5±1.4
Cardiac index (L·min^{-1}·m^{-2})	116	2.8±0.8	3±0.8	2.7±0.8
PCWP (mmHg)	139	12±3	12±3	12±3
Treatments	139			
Monotherapy		137 (99)	69 (100)	68 (97)
Bitherapy		2 (1)	0 (0)	2 (3)
Delay to re-evaluation (days)	118	150±115	164±144	134±69

Data are presented as n, n (%) or mean±SD. OLD: obstructive lung disease; PH: pulmonary hypertension; ILD: interstitial lung disease; BMI: body mass index; NYHA FC: New York Heart Association functional class; 6MWD: 6-min walk distance; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; TLC: total lung capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; NT-proBNP: N-terminal pro-brain natriuretic peptide; BNP: brain natriuretic peptide; mPAP: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance; PCWP: pulmonary capillary wedge pressure.

Pulmonary function tests did not improve after PAH-targeted therapy. Absolute FEV_1 variation was −0.2% pred (p=0.53), whereas FVC increased by 0.3% pred (p=0.88). D_{LCO} was unchanged with a nonsignificant decrease of −0.4% pred (p=0.63). Oxygen supplementation significantly deteriorates with a mean variation of +0.6 L·min^{-1} (p<0.001) under therapy (table 2).

Predictive factors for response

Baseline mPAP was higher in responder patients than the nonresponders, with 46 mmHg *versus* 42 mmHg, respectively, in the two groups, but it was nonsignificant (p=0.09) (table 3). Initial pathology group tended not to be a predictive factor for response, with 29% responders in the obstructive lung disease group *versus* 42% in the ILD group (p=0.26).

Baseline preserved pulmonary function tests were not associated with a response to PAH-targeted therapy (table 3).

In the obstructive lung disease-PH group, we didn't find any predictive factor for response to treatment on 6MWD depending on age, sex, baseline NYHA FC, BNP, NT-proBNP, baseline FEV_1 and FVC, baseline PVR, mPAP and cardiac index.

TABLE 2 Primary and secondary end-points

	Patients	Baseline	Overall		OLD-PH group		ILD-PH group	
			Change	p-value	Change	p-value	Change	p-value
6MWD (m)	77	310	+1.5±82	0.59	+7.2±63	0.52	−5±99	0.90
LTOT (L·min^{-1})	122	2	+0.6±1.7	<0.001*	+0.15±1.2	0.27	+1.2±2	0.001*
PVR (Wood Units)	105	6.9	−1±2.8	<0.001*	−1.2±2.1	<0.001*	−0.9±3.5	0.0052*
mPAP (mmHg)	116	44	−4±8	<0.001*	−5±7.9	<0.001*	−3±8	0.013*
Cardiac output (L·min^{-1})	109	5	+0.2±1.4	0.18	+0.01±1.2	0.76	+0.3±1.5	0.15
Cardiac index (L·min^{-1}·m^{-2})	90	2.8	+0.1±0.8	0.33	-0.03±0.8	0.86	+0.1±0.8	0.28
FEV_1 (% pred)	111	48	−0.2±7	0.53	+0.3±6	0.78	−0.8±7	0.29
FVC (% pred)	111	59	+0.3±12	0.88	+0.8±14	0.70	−0.3±9	0.39
D_{LCO} (% pred)	38	24	−0.4±6	0.63	+0.6±5	0.84	−0.9±6	0.46
NT-proBNP (pg·mL^{-1})	56	1023	+50±1764	0.08	−187±694	0.3	+256±2323	0.19
BNP (pg·mL^{-1})	48	102	+14±156	0.68	−22±40	0.0017*	+61±227	0.1

Data are presented as n or mean±SD, unless otherwise stated. OLD: obstructive lung disease; PH: pulmonary hypertension; ILD: interstitial lung disease; 6MWD: 6-min walk distance; LTOT: long-term oxygen therapy; PVR: pulmonary vascular resistance; mPAP: mean pulmonary arterial pressure; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; NT-proBNP: N-terminal pro-brain natriuretic peptide; BNP: brain natriuretic peptide. *: p<0.05.

In the ILD-PH group, baseline PVR was found to be a predictive factor for response: responder patients had baseline PVR of 7.3 Wood Units whereas nonresponders had PVR of 6.1 Wood Units (p=0.038).

Survival and safety

57 (41%) patients died during our study. Median (95% CI) overall survival from the start of the treatment was 39.6 (30.1–67.0) months (figure 1). In obstructive lung disease, median survival was 67 (33.6–not applicable) months, whereas in ILD it was 21.1 (12.1–50.1) months (figure 2). There was a significant difference between populations (p=0.001) with a greater risk of death among the ILD population (hazard ratio 2.76, 95% CI 1.61–4.92; p=0.0002). Age, mPAP, cardiac index, PVR and FEV_1 seem to be predictive factors of death in this population (table 4). Main causes of death were respiratory failure (21% of deaths) and heart failure (14% of deaths). Data are missing for other patients.

25 (18%) patients had to stop treatment due to intolerance (figure 3) and there was no difference between obstructive lung disease and ILD groups (p=0.23). The primary cause of treatment discontinuation was

TABLE 3 Comparison of responder and nonresponder populations to targeted pulmonary arterial hypertension therapy on 6-min walk distance (univariate analysis) in the overall population

	Patients	Responders	Nonresponders	OR (95% CI)	p-value
Age (years)	77	61.5±10	58.5±10	1.03 (0.98–1.08)	0.24
Chronic lung disease					0.26
OLD	41	12 (29)	29 (71)	1	
ILD	36	15 (42)	21 (58)	1.7 (0.67–4.37)	
BNP (pg·mL^{-1})	35	98±130	77±82	1 (1–1.01)	0.69
NT-proBNP (pg·mL^{-1})	39	421±673	353±650	1 (1–1)	0.78
PVR (Wood Units)	74	7.4±3.5	6.2±2	1.18 (0.99–1.44)	0.16
mPAP (mmHg)	77	46±10	42±6	1.07 (1.01–1.14)	0.09
Cardiac index (L·min^{-1}·m^{-2})	65	2.8±1	2.8±0.6	1.02 (0.51–1.98)	0.49
FVC (% pred)					0.35
⩾70	24	10 (42)	14 (58)	1.6 (0.59–4.3)	
<70	52	16 (31)	36 (69)	1	
FEV_1 (% pred)					0.35
⩾60	24	10 (42)	14 (58)	1.6 (0.59–4.3)	
<60	52	16 (31)	36 (69)	1	

Data are presented as n, mean±SD or n (%), unless otherwise stated. OLD: obstructive lung disease; ILD: interstitial lung disease; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-BNP; PVR: pulmonary vascular resistance; mPAP: mean pulmonary arterial pressure; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s.

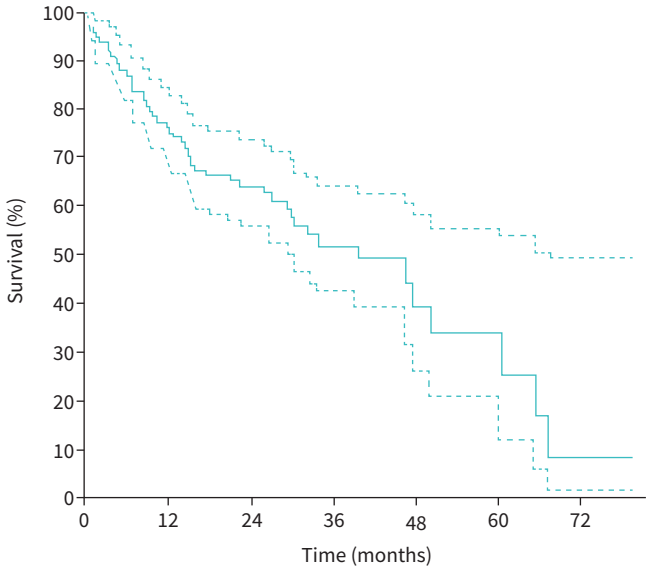

FIGURE 1 Kaplan–Meier survival estimates (with 95% CI shown in dashed lines) for the overall population.

increased dyspnoea (n=13, 52%) followed by peripheral oedema (n=4, 16%), hypotension (n=4, 16%) and dizziness (n=4, 16%). No risk factor for treatment discontinuation was found among age, underlying pulmonary disease, sex, NYHA functional class, lung function, BNP, mPAP, cardiac index and PVR (table 5).

Mean duration of treatment was 147 days. 93 (67%) patients were treated for ⩾3 months. A treatment duration <3 months was associated with poorer survival (hazard ratio 2.73, 95% CI 1.57–4.73; p=0.0005).

Discussion

PH is a frequent complication of CLD and is associated with a poor prognosis, impaired quality of life, increased risk of exacerbation, decreased exercise capacity and a higher mortality [3–9, 30].

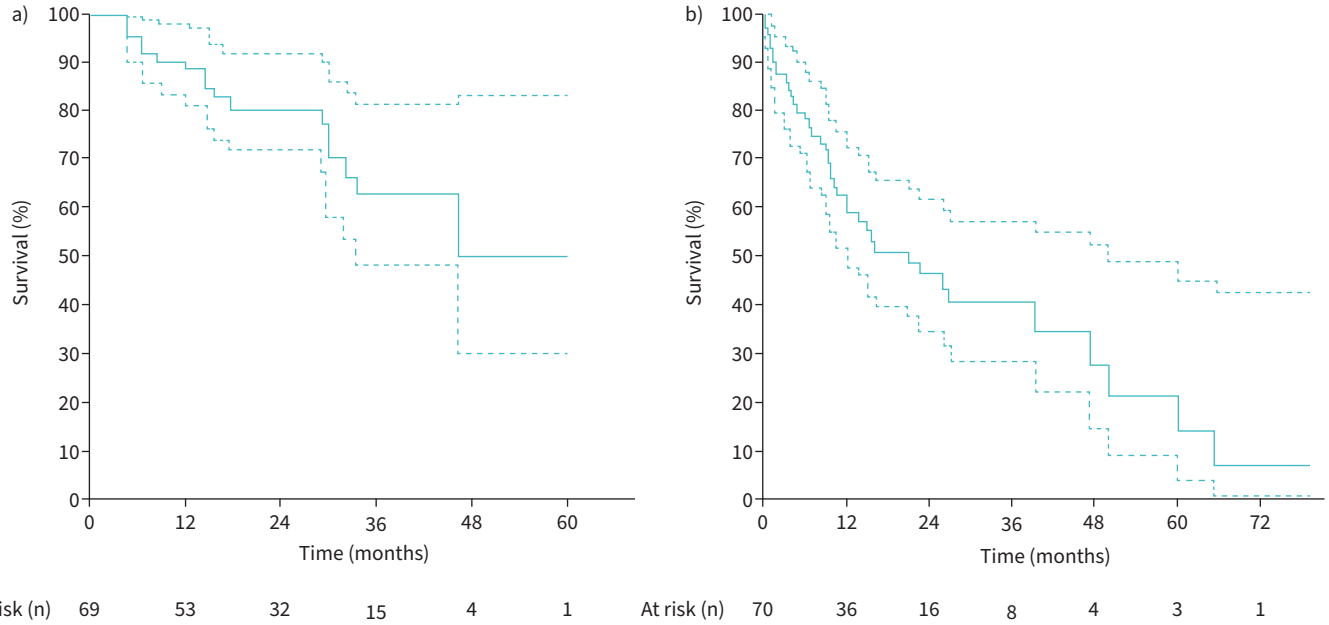

FIGURE 2 Kaplan–Meier survival estimates (with 95% CI shown in dashed lines) for the a) obstructive lung disease and b) interstitial lung disease populations. Log rank p=0.00018.

TABLE 4 Factors predictive of death

	Patients (n)	Hazard ratio (95% CI)	p-value
Sex			
Female	53	1	NA
Male	86	1.71 (0.99–3.06)	0.06
Age (years)	139	1.08 (1.05–1.12)	<0.0001*
Chronic lung disease			
OLD	69	1	NA
ILD	70	2.76 (1.61–4.92)	0.0002*
NYHA FC			
I	2	1	NA
II	13	0.26 (0.04–2.68)	0.21
III	51	0.47 (0.12–4.32)	0.43
IV	52	0.91 (0.24–8.2)	0.91
Baseline BNP ($pg \cdot mL^{-1}$)	62	1 (1–1)	0.06
Baseline NT-proBNP ($pg \cdot mL^{-1}$)	72	1 (1–1)	0.21
Treatment class sildenafil/tadalafil			
0	11	1	NA
Sildenafil	80	0.77 (0.35–1.96)	0.55
Tadalafil	48	0.73 (0.3–2.0)	0.52
Baseline mPAP (mmHg)	139	1.03 (1–1.06)	0.02*
Baseline cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	116	0.56 (0.36–0.86)	0.006*
Baseline PVR (Wood Units)	136	1.12 (1.04–1.19)	0.004*
Baseline FEV_1 (% pred)			
<70	91	1	NA
⩾70	41	1.81 (1.03–3.15)	0.04*
Baseline FVC (% pred)			
<60	89	1	NA
⩾60	42	1.6 (0.92–2.75)	0.1

OLD: obstructive lung disease; ILD: interstitial lung disease; NYHA FC: New York Heart Association functional class; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-BNP; mPAP: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; NA: not applicable. *: p<0.05.

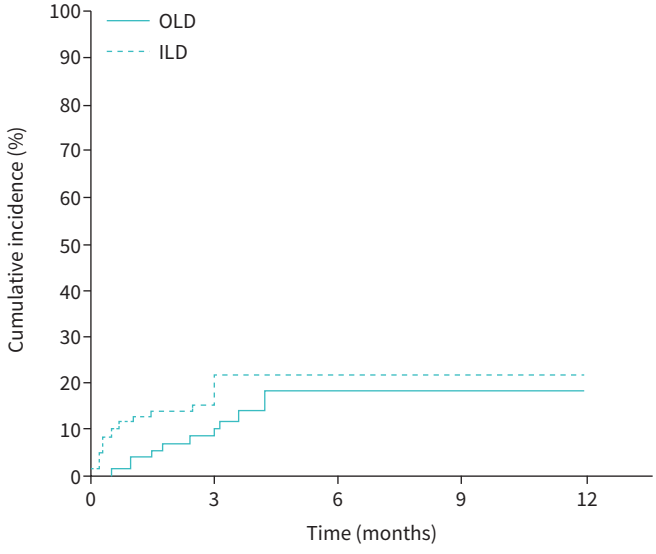

FIGURE 3 Cumulative incidence of discontinuation of pulmonary arterial hypertension targeted therapy in the obstructive lung disease (OLD) and interstitial lung disease (ILD) populations. Comparison made using univariate Fine–Gray regression. p=0.23.

TABLE 5 Factors predictive of treatment discontinuation

	Patients (n)	Hazard ratio (95% CI)	p-value
Sex			
Female	53	1	NA
Male	86	0.98 (0.45–2.15)	0.96
Age (years)	139	1.02 (0.97–1.06)	0.48
Chronic lung disease			
OLD	69	1	NA
ILD	70	1.62 (0.74–3.55)	0.22
Baseline BNP (pg·mL^{-1})	62	1 (1–1.01)	0.27
Baseline NT-proBNP (pg·mL^{-1})	72	1 (1–1)	0.13
Treatment class sildenafil/tadalafil			
0	11	1	NA
Sildenafil	80	1.84 (0.22–15.26)	0.57
Tadalafil	48	2.11 (0.25–17.72)	0.49
Baseline mPAP (mmHg)	139	0.97 (0.92–1.03)	0.37
Baseline cardiac index (L·min^{-1}·m^{-2})	116	1.14 (0.63–2.03)	0.66
Baseline PVR (Wood Units)	136	0.94 (0.8–1.12)	0.49
Baseline FVC (% pred)			
⩾70	91	0.80 (0.32–1.97)	0.62
<70	41	1	NA
Baseline FEV_1 (% pred)			
⩾60	42	0.62 (0.23–1.62)	0.32
<60	89	1	NA

OLD: obstructive lung disease; ILD: interstitial lung disease; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-BNP; mPAP: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; NA: not applicable.

In our cohort, specific treatment of severe CLD-PH did not improve exercise capacity quantified by the 6MWD. One-third of the patients responded to treatment with an improvement of ⩾30 m in 6MWD at re-evaluation. There was a statistically significant improvement in haemodynamics (mPAP and PVR) with PAH-targeted therapies. Nearly one-fifth of patients stopped treatment due to intolerance.

International guidelines [1] state that there are insufficient data about targeted PAH therapies for CLD-PH and suggest assessing only severe CLD-PH for individual-based treatment. However, most trials studied these treatments in heterogeneous populations including mild-to-severe CLD-PH [12–16], and many studies used only transthoracic echocardiography to detect PH without performing RHC for all patients [22–25].

To our knowledge our study contains one of the largest "real-life" cohorts of severe CLD-PH treated, and re-evaluated, with PAH-targeted therapy.

As published previously, 6MWD was used as primary end-point because it reflects exercise capacity [12, 31, 32]. Interestingly, 6MWD was measured by the same physiotherapists through the study, which enhances its reproducibility. Another strength is that we only selected patients with severe PH defined with haemodynamic criteria using RHC.

However, our study has some limits, due to its retrospective and observational design. Firstly, we are aware that our population is heterogeneous, including various pathological entities and patterns, mainly in the ILD group. Secondly, despite the relatively high number of patients, the primary end-point could be achieved for just over half of them (n=77, 55% of the included patients). Indeed, some patients were unable to perform a 6MWD at re-evaluation due to an important worsening of their clinical respiratory condition; this loss of information may have contributed to a difficult interpretation of the results and a nonsignificant difference from baseline values. Moreover, we were unable to perform multivariate analyses for predictive factors. Finally, it is important to note that, as reported in the literature in this context, we only used oral therapies, whereas in a multicentre, randomised, double-blind, placebo-controlled trial, treprostinil showed a statistically and clinically significant improvement in 6MWD of 31.1 m among CLD-PH when administered by inhalation four times daily *versus* placebo [12].

Regarding the results, our study is consistent with previously published studies. In a larger prospective multicentre French cohort of severe COPD-PH, there was no strong evidence of benefit of PAH-targeted therapy in terms of improvement in exercise tolerance and clinical symptoms [33]. A meta-analysis of 376 mild-to-severe CLD-PH patients did not find any difference in 6MWD after 3 months of treatment with any oral targeted PAH therapy [19].

However, some studies showed an improvement in 6MWD with targeted PAH therapies. In a randomised controlled trial with sildenafil *versus* placebo, there was a significant improvement of 190 m on 6MWD among 37 COPD patients. Nevertheless, not all patients had undergone RHC and groups were not comparable because of a difference of 55 m on 6MWD at baseline, which may misrepresent the difference between groups [24]. A meta-analysis of 365 patients with COPD showed an improvement of 66 m on 6MWD after treatment with oral targeted PAH therapy (sildenafil or bosentan, depending on the studies), but these data were limited by a very high heterogeneity with inconstant PH severity [21].

These contradictory results may be explained by the fact that in patients with CLD, exercise limitation is not only related to cardiocirculatory impairment, but also to insufficient ventilatory reserve [11], whereas targeted PAH therapies only improve circulatory limitation. It could be interesting to determine the aetiology of exercise capacity limitations using cycle ergometer in order to assess the interest of targeted PAH therapy in patients presenting only a predominant cardiocirculatory limitation (defined as vascular phenotype).

A subgroup of our patient cohort had a clinical benefit on 6MWD. This subgroup could present such a vascular phenotype. This concept has emerged from a very few retrospective studies for a subset of COPD patients who had a severe PH, with the following characteristics: nonsevere airflow limitation, profound hypoxaemia, normo- or hypocapnia, very low D_{LCO} and high level of dyspnoea at exercise, and then a poor prognosis [11, 17, 34]. Several lines of evidence suggested that CLD promoted a pulmonary vascular disease regardless of lung function impairment without any correlation between severity of PH and pulmonary function tests [35]. Pathological examination of IPF patients' lungs shows evidence of vascular remodelling (as in PAH) in areas of normal lung [36]. So, we can believe that some vascular phenotype may benefit from PH treatment, hence the importance of identifying these subgroups of patients.

Nathan *et al*. [10] proposed considering targeted PAH therapy only in some CLD-PH patients, mainly those with limited CLD (mild-to-moderate obstructive/restrictive lung disease defined by FEV_1 >60% pred and FVC >70% pred and minimal parenchymal computed tomography changes) or those with severe PH documented by RHC. For this reason, we tried to assess whether FEV_1 and FVC alteration could be a surrogate factor for response to treatment. However, in our study, airway limitation does not seem to be a predictive factor of response on 6MWD.

Concerning haemodynamic parameters, our study seems to be concordant with most studies showing a modest improvement of mPAP or PVR [16, 20, 37, 38]. However, these results must be taken with caution, because after diagnosing PH, patients were optimised with diuretics, sodium-restricted diet, LTOT and other general treatment such as supervised rehabilitation if needed [1]. All these changes can themselves explain haemodynamic improvement. Moreover, a decrease of only 3.9 mmHg on mPAP and 1 Wood Unit on PVR may not be clinically relevant, given that there was no improvement on exercise capacity.

However, it would be interesting to assess the benefit of these treatments on patients with severe CLD-PH who are eligible for lung transplantation with a view to decrease peri- and post-operative mortality due to PH, but without delaying time to transplantation.

According to the latest recommendations [39], classification of severity is now based on evaluation of PVR (with a cut-off of 5 Wood Units). It would be interesting to assess the efficacy of PAH-targeted therapies in this population.

Regarding safety, 18% of our patients stopped treatment due to adverse events. These data, combined with the efficacy of therapy, raise the question of the relevance of such treatments for these patients.

Conclusion

Oral targeted PAH therapies do not improve exercise capacity assessed on 6MWD, but could improve haemodynamic parameters in patients with severe CLD-PH. A preserved pulmonary function does not seem to be a predictive factor of response. However, some patients were responders to PAH-targeted

therapy, suggesting that some predictive criteria for response may be assessed and proposed. A treatment duration of >3 months seems to be associated with greater survival. Because of the several mechanisms involved, it could be interesting to assess potential responder patients using a cycle ergometer to identify patients with main cardiocirculatory limitation before therapy initiation. Finally, it is important to assess targeted PAH therapies using the new classification of PH severity.

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