Management and long-term outcomes of sarcoidosis-associated pulmonary hypertension

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Severe pulmonary hypertension remains a life-threatening complication of sarcoidosis in the modern management era http://ow.ly/fIln30etYkE

Cite this article as: Boucly A, Cottin V, Nunes H, *et al*. Management and long-term outcomes of sarcoidosis-associated pulmonary hypertension. *Eur Respir J* 2017; 50: 1700465 [https://doi.org/10.1183/13993003.00465-2017].

ABSTRACT Studies reporting the effects of modern strategies with pulmonary arterial hypertension (PAH)-targeted therapies in sarcoidosis-associated pulmonary hypertension (S-APH) are limited.

Clinical and haemodynamic data from newly diagnosed patients with severe S-APH (mean pulmonary artery pressure (mPAP) >35 mmHg or mPAP 25–35 mmHg with cardiac index <2.5 L·min^{-1}·m^{-2}) were collected from the French Pulmonary Hypertension Registry between 2004 and 2015.

Data from 126 patients with severe S-APH were analysed (mean±SD age 57.5±11.6 years, 74% radiological stage IV). 97 patients (77%) received PAH-targeted therapy and immunosuppressive therapy was initiated or escalated in 33 patients at the time of pulmonary hypertension diagnosis. Four months after PAH-targeted therapy initiation, mean±SD pulmonary vascular resistance decreased from 9.7±4.4 to 6.9±3.0 Wood units ($p<0.001$), without significant improvement in exercise capacity. Among the 11 patients treated only with immunosuppressive therapy, a haemodynamic improvement was observed in four patients, including two with compressive lymph nodes. After a median follow-up of 28 months, 39 patients needed PAH-targeted therapy escalation, nine underwent lung transplantation and 42 had died. Survival at 1, 3 and 5 years was 93%, 74% and 55%, respectively.

PAH-targeted therapy improved short-term pulmonary haemodynamics in severe S-APH without change in exercise capacity. Immunosuppressive therapy improved haemodynamics in selected patients. Pulmonary hypertension in sarcoidosis remains associated with a poor prognosis.

This article has supplementary material available from erj.ersjournals.com

Received: March 06 2017 | Accepted after revision: July 27 2017

Support statement: This study was supported in part by the Département Hospitalo-Universitaire Thorax Innovation (TORINO), the Laboratoire d'Excellence en Recherche sur le Médicament et l'Innovation Thérapeutique (LERMIT) and the Projet Hospitalier de Recherche Clinique (PHRC) HYpertension pulmonaire des Pneumopathies Interstitielles Diffuses (HYPID).

Conflict of interest: Disclosures can be found alongside this article at erj.ersjournals.com

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Introduction

Pulmonary vascular involvement occurs frequently in sarcoidosis and may lead to pulmonary hypertension by multiple mechanisms [1, 2]. The prevalence of pulmonary hypertension in sarcoidosis varies between studies according to the characteristics of the study population and the methods used for diagnosis and definition of pulmonary hypertension. In studies involving symptomatic patients or those listed for lung transplantation, the prevalence of pre-capillary pulmonary hypertension, defined by mean pulmonary artery pressure (mPAP) >25 mmHg with pulmonary arterial wedge pressure (PAWP) <15 mmHg, is 5–74% [3–9]. In sarcoidosis, complex pathophysiological interactions may occur between the pulmonary vasculature and parenchymal, mediastinal and cardiovascular compartments. Elevation of pulmonary pressures can be attributed to direct granulomatous involvement of pulmonary vessels, or may be the indirect consequence of advanced parenchymal destruction or compressive mediastinal infiltration. In the updated classification of pulmonary hypertension, sarcoidosis appears as a separate entity within the fifth subgroup that comprises a heterogeneous collection of diseases with uncertain pathophysiological mechanisms leading to pulmonary hypertension [1, 2]. In all these conditions, including sarcoidosis, pulmonary hypertension is a complication with considerable functional and prognostic consequences. Pulmonary hypertension confers a poor prognosis in sarcoidosis patients with an 8- to 10-fold increase in mortality [3, 10]. Therefore, screening for pulmonary hypertension, accurate diagnosis of pulmonary hypertension and selection of an optimal treatment strategy are important issues. However, recommendations on specific management of pulmonary hypertension associated with sarcoidosis are lacking. Effects of immunosuppressive and pulmonary arterial hypertension (PAH)-targeted therapies are understudied, and methodological issues limit the results of small retrospective studies. Only one prospective randomised controlled trial reported a beneficial effect of bosentan on pulmonary haemodynamics at 16 weeks, although without any improvement in exercise capacity [11]. Finally, there are few observations on the effect of immunosuppressive therapies on pulmonary hypertension associated with sarcoidosis.

The objectives of this observational study were to report the characteristics of a large cohort of patients with severe pulmonary hypertension associated with sarcoidosis and to analyse their long-term outcomes in the modern management era.

Methods

Study population

Data from all newly diagnosed (*i.e.* incident) sarcoidosis-associated pulmonary hypertension (S-APH) patients referred to the French Reference Centre for Severe Pulmonary Hypertension (Université Paris-Sud, Le Kremlin-Bicêtre, France) and 17 expert centres from the French Pulmonary Hypertension Network between January 2004 and December 2014 were collected from the web-based French Pulmonary Hypertension Registry (PAH Tool; INOVULTUS, Santa Maria da Feira, Portugal). 31 patients had been included in the prospective observational HYPID study (ClinicalTrials.gov: NCT01443598 and NCT02799771).

All patients had sarcoidosis defined by standard criteria (American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and Other Granulomatous Disorders) [12], and pre-capillary pulmonary hypertension was defined by mPAP ⩾25 mmHg and PAWP ⩽15 mmHg measured by right heart catheterisation (RHC) [1, 2]. Only patients with severe pulmonary hypertension, defined by mPAP >35 mmHg or mPAP 25–35 mmHg with cardiac index <2.5 $L \cdot min^{-1} \cdot m^{-2}$ [1, 2] were included in the

study. All patients underwent extensive investigations to identify additional possible causes or risk factors for pulmonary hypertension [5]. Exclusion criteria were chronic thromboembolic pulmonary hypertension, pulmonary hypertension related to left heart diseases and PAH associated with other conditions, including HIV infection, portal hypertension, congenital left-to-right shunts, connective tissue diseases, and exposure to drugs (*e.g.* anorectic drugs) and toxins. In addition to RHC, baseline evaluation included physical examination, assessment of modified World Health Organization (WHO)/New York Heart Association (NYHA) functional class, routine blood tests, nonencouraged 6-min walk test (6MWT), pulmonary function tests, arterial blood gases and high-resolution computed tomography. When pulmonary vascular compression was suspected (fibrosing mediastinitis or extrinsic compression by lymph nodes), results from pulmonary angiograms and ^{18}F-2-fluoro-2-deoxy-D-glucose (^{18}F-FDG)-positron emission tomography (PET) scans were collected if available.

The study complied with the Declaration of Helsinki. Although French law does not require ethics committee approval or informed consent for retrospective data collection, the data collected were anonymised and complied with the requirements of the Commission Nationale Informatique et Liberté, the organisation dedicated to privacy, information technology and civil rights in France. The committee approved the methods used to collect and analyse data on May 24, 2003 (approval 842063).

Treatment regimens

All patients received nonspecific supportive therapies in accord with current guidelines, *i.e.* diuretics to control signs and symptoms of fluid retention, and long-term oxygen therapy if hypoxaemia was present [5]. Choice of PAH-targeted medications, *i.e.* endothelin receptor antagonists, phosphodiesterase type 5 inhibitors or prostanoids, was left to the discretion of the treating physician. In the absence of formal recommendations for patients with S-APH, the choice of PAH-targeted therapy was based according to the severity of pulmonary hypertension and the extent of parenchymal involvement. The specific management of sarcoidosis with immunosuppressive medications (including corticosteroids) was also left to the discretion of the treating physician.

Study assessments

Patients were assessed at baseline (*i.e.* time of pulmonary hypertension diagnosis) and follow-up visits performed every 6 months, on average. Visits included a reassessment of WHO/NYHA functional class, 6-min walk distance (6MWD) and cardiopulmonary haemodynamics by RHC. The last follow-up visit was defined as the time-point where a complete evaluation (including RHC) had been conducted. If patients were unable to perform a 6MWT at baseline or at any of the follow-up visits, a 6MWD of 0 m was recorded. Vital status was ascertained by chart review or telephone contact in May 2015.

Statistical analysis

Analyses were performed using the StatEL statistical package in Microsoft Excel 2007 (Ad Science, Paris, France). Data are expressed as mean±SD for normally distributed variables and as median (interquartile range (IQR)) for nonnormally distributed variables. Comparisons of 6MWD and haemodynamic variables obtained at baseline and first follow-up visit were made using the paired-t-test for normally distributed variables and the Wilcoxon signed-rank test for nonnormally distributed variables. *Post hoc* comparisons were made using Fisher's exact test. The Chi-squared test for independence was used to compare differences between WHO/NYHA functional class assessed at baseline and first follow-up visit. A p-value <0.05 was considered statistically significant.

Analysis of overall survival was performed using an intention-to-treat approach. Survival time was calculated from the date of the initial diagnostic RHC until May 31, 2015, or the date of death or lung transplantation. The Kaplan–Meier method was used to estimate survival at each interval. Patients who underwent lung transplantation were censored at the date of transplantation. Patients who were lost to follow-up were censored at the last available visit.

Univariate analysis based on the Cox proportional hazards model was used to examine the relationship between survival and selected baseline demographic, lung function and haemodynamic variables. Results are expressed as hazard ratios with 95% confidence intervals. Multivariate Cox proportional hazards regression analysis was used to examine the independent effect of each variable on survival, controlling for possible confounding variables.

Results

Patient demographics and characteristics at the time of pulmonary hypertension diagnosis

156 patients with sarcoidosis and pre-capillary pulmonary hypertension were identified in the French Pulmonary Hypertension Registry between January 2004 and December 2014. Among them, 126 patients

had mPAP >35 mmHg or mPAP 25–35 mmHg with cardiac index <2.5 $L \cdot min^{-1} \cdot m^{-2}$ and were included in the study. Patient disposition is summarised in figure 1. Baseline demographic and clinical characteristics are summarised in table 1. The median time between the diagnosis of sarcoidosis and that of pulmonary hypertension was 17 years. The sex ratio was ∼1:1 and the mean age 57.5 years. The majority of patients (72%) had radiological stage IV sarcoidosis at the time of pulmonary hypertension diagnosis. 30 patients (24%) had a severe restrictive pattern with forced vital capacity (FVC) <50% predicted.

Initial management

Initial therapy is summarised in figure 1. PAH-targeted medications were prescribed in 97 patients (77%). Most of them (n=83) received initial monotherapy, including 60 with an endothelin receptor antagonist (bosentan (n=54) or ambrisentan (n=6)), 20 with a phosphodiesterase type 5 inhibitor (sildenafil (n=15) or tadalafil (n=5)), two with intravenous infusion of epoprostenol and one with inhaled iloprost. 14 patients were initiated with combination therapy according to the following distribution: bosentan and sildenafil (n=8) or tadalafil (n=1), ambrisentan and sildenafil (n=2) or tadalafil (n=1), bosentan and *i.v.* epoprostenol (n=1), or subcutaneous treprostinil (n=1). At the time of pulmonary hypertension diagnosis, 51 patients (40%) received background immunosuppressive therapy, including corticosteroids in most of them. In 33 patients (25 on background immunosuppressive therapy and eight treatment-naive patients), immunosuppressive therapy was initiated or escalated after the diagnosis of pulmonary hypertension was made. Among these 33 patients, 22 were treated in combination with PAH-targeted medications and 11 received immunosuppressive therapy or corticosteroid alone. 18 patients received neither PAH-targeted nor immunosuppressive therapy.

Treatment response at first follow-up visit

Repeat clinical and haemodynamic assessments were performed after a median (IQR) period of 4.5 (4.0–6.7) months in 81 out of the 97 patients initiated on PAH-targeted therapy. 16 patients were not reassessed by RHC in the first year due to death (n=7) or lung transplantation before reassessment (n=2). In addition, four patients were reassessed by echocardiography only and three were lost to follow-up. In the 81 patients who had been reassessed, there were significant improvements from baseline in haemodynamic variables with an increase in cardiac index by 0.3 $L \cdot min^{-1} \cdot m^{-2}$ and a decrease in pulmonary vascular resistance (PVR) by 29% (table 2). In addition there was an improvement in WHO/NYHA functional class. However, there was no significant improvement in 6MWD. No difference was

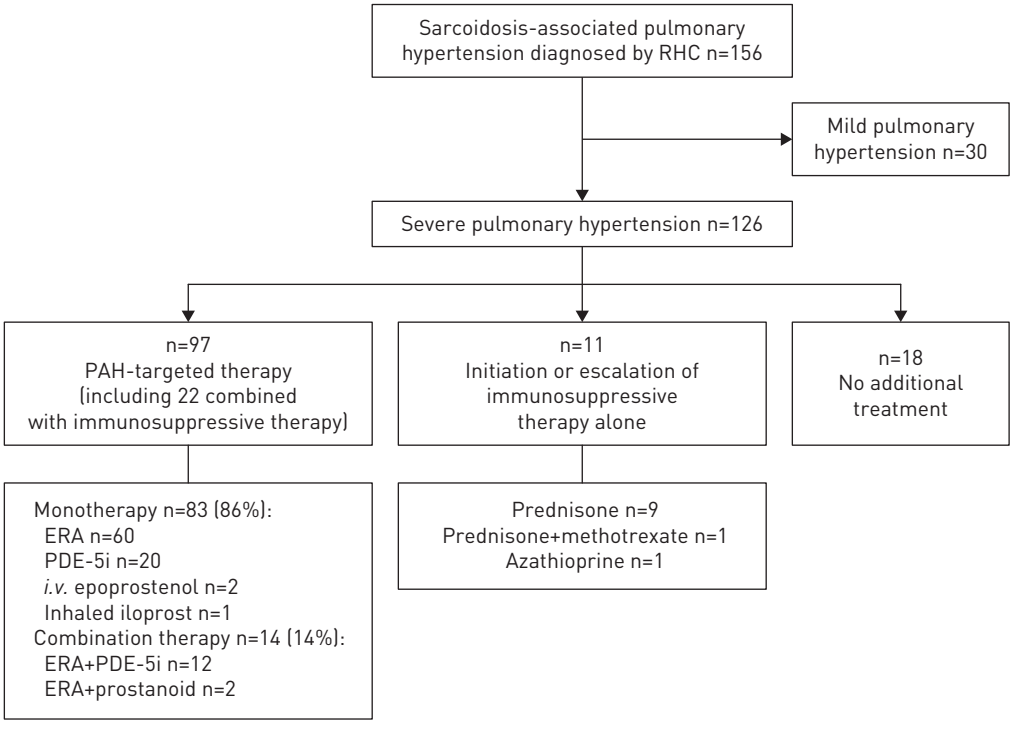

FIGURE 1 Patient disposition and initial therapy. RHC: right heart catheterisation; PAH: pulmonary arterial hypertension; ERA: endothelin receptor antagonist; PDE-5i: phosphodiesterase type 5 inhibitor.

TABLE 1 Demographics and baseline characteristics of patients with newly diagnosed severe sarcoidosis-associated pulmonary hypertension

Patients	126
Male/female	65 (52)/61 (48)
Age years	57.5±10.6
BMI kg·m^{-2}	25.5±6.6
Tobacco exposure	42 (33)
Time between sarcoidosis and pulmonary hypertension diagnosis months	204 (59–313)
Radiological stage	
I	6 (5)
II	22 (17)
III	7 (6)
IV	91 (72)
WHO/NYHA functional class	
I–II	21 (17)
III	79 (63)
IV	26 (20)
6MWD m	319±143
Borg dyspnoea scale	4.9±2.3
Haemodynamics	
RAP mmHg	7±5
mPAP mmHg	46±10
PAWP mmHg	9±4
Cardiac index L·min^{-1}·m^{-2}	2.6±0.8
PVR Wood units	8.8±4.3
S_{vO_2} %	63.4±8.9
Lung function tests	
FVC % pred	64±21
FEV_1 % pred	55±22
K_{CO} % pred	54±23
Long-term oxygen therapy	68 (54)

Data are expressed as n, n (%), mean±SD or median (interquartile range). BMI: body mass index; WHO: World Health Organization; NYHA: New York Heart Association; 6MWD: 6-min walk distance; RAP: right atrial pressure; mPAP: mean pulmonary artery pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; S_{vO_2}: mixed venous oxygen saturation; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; K_{CO}: transfer coefficient of the lung for carbon monoxide.

found in both 6MWD and PVR changes on therapy according to radiological stage of sarcoidosis (stage IV *versus* others) or severity of restrictive physiology (FVC ⩽50% *versus* >50% predicted) (figure 2).

11 patients were treated with immunosuppressive therapy (corticosteroid, methotrexate or azathioprine) alone and were reassessed after 4–6 months. Individual results are shown in table 3. Five patients had extrinsic compression of pulmonary arteries by lymph nodes or fibrosing mediastinitis. There was an increased uptake of ^{18}F-FDG on PET scan for three of these patients (two with compressive lymph nodes and one with fibrosing mediastinitis). In the two patients with compressive lymph nodes, a haemodynamic improvement was observed after immunosuppressive therapy. In contrast, there was no improvement in the three patients with fibrosing mediastinitis. In two patients who had severe pulmonary hypertension without evidence of pulmonary vessel compression, immunosuppressive therapy alone improved haemodynamics, but not WHO/NYHA functional class or 6MWD.

Long-term follow-up

Over a median (IQR) follow-up period of 28 (11–56) months, 42 patients (33%) died, nine underwent lung transplantation and 39 needed treatment escalation with PAH-targeted medications. Overall survival rates were 93%, 74% and 55% at 1, 3 and 5 years, respectively (figure 3). The median survival time was 6.8 years.

Despite a better haemodynamic profile at baseline, patients who did not receive any PAH-targeted medication during follow-up had a similar survival as patients initiated with PAH-targeted drugs (supplementary table S1 and supplementary figure S1).

Baseline prognostic factors

The results of univariate analysis of baseline variables and survival are shown in table 4. Mortality was not associated with age, sex, radiological stage or any haemodynamic variables. WHO/NYHA functional class

TABLE 2 Effects of pulmonary arterial hypertension-targeted therapy on World Health Organization (WHO)/New York Heart Association (NYHA) functional class, exercise capacity and haemodynamics at first follow-up visit in patients with severe sarcoidosis-associated pulmonary hypertension[#]

	Baseline	First follow-up visit[¶]	Difference	p-value
WHO/NYHA functional class I–II/III/IV	11/52/18	26/45/10		0.01
6MWD m	311±127	324±138	+13 m	0.33
RAP mmHg	7±4	6±4	−14%	0.007
mPAP mmHg	48±9	42±11	−13%	<0.00001
Cardiac index L·min^{-1}·m^{-1}	2.6±0.8	2.9±0.8	+12%	<0.00001
PVR Wood units	9.7±4.4	6.9±3.0	−29%	<0.00001

Data are expressed as n or mean±SD, unless otherwise stated. 6MWD: 6-min walk distance; RAP: right atrial pressure; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance. [#]: n=81; [¶]: median (interquartile range) 4.5 (4.0–6.7) months.

IV, 6MWD and reduced FVC or transfer coefficient of the lung for carbon monoxide were associated with a poor survival. A multivariate Cox proportional hazards regression analysis with stepwise selection was performed including variables that were associated with mortality on univariate analysis with a p-value <0.10. In multivariate analysis, only 6MWD remained independently associated with mortality (hazard ratio 0.995, 95% CI 0.991–0.999).

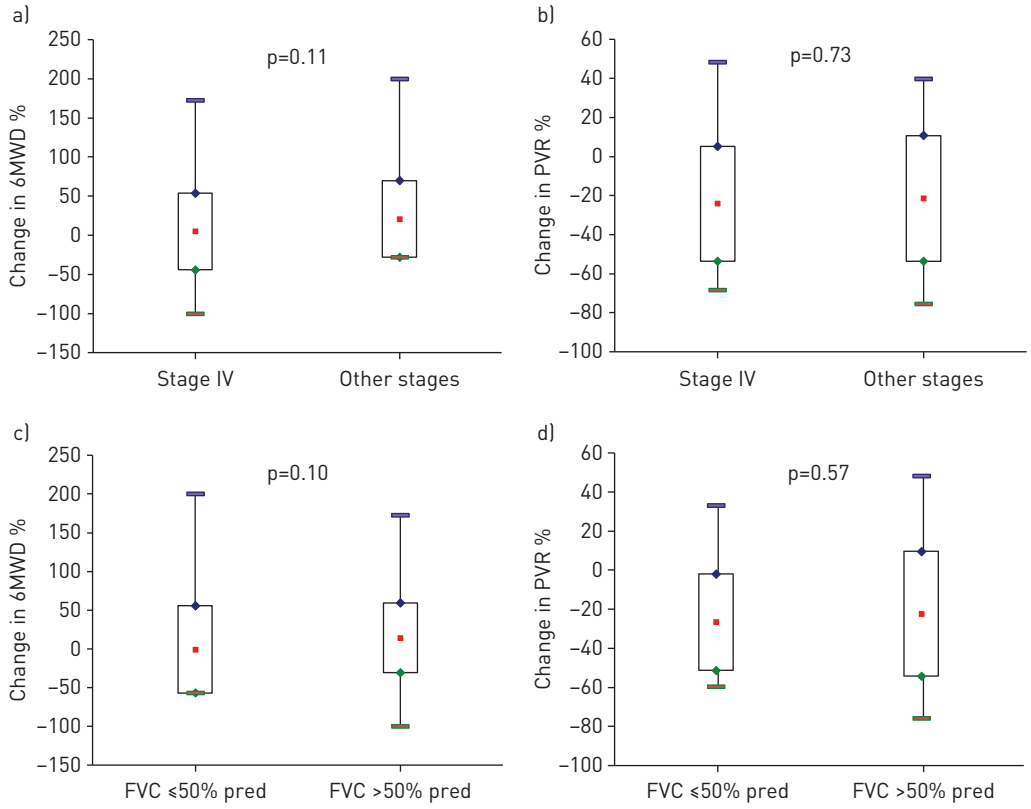

FIGURE 2 Box plots of change in 6-min walk distance (6MWD) and pulmonary vascular resistance (PVR) according to a, b) radiological stage of sarcoidosis or c, d) severity of restrictive physiology (forced vital capacity (FVC)). a) Change in 6MWD according to radiological stage of sarcoidosis (stage IV *versus* others): +5±49% *versus* +21±49%; p=0.11. b) Change in PVR according to radiological stage of sarcoidosis (stage IV *versus* others): −24±29% *versus* −22±32%; p=0.73. c) Change in 6MWD according to FVC (⩽50% *versus* >50% predicted): −1±56% *versus* +14±45%; p=0.10. d) Change in PVR according to FVC (⩽50% *versus* >50% predicted): −22±32% *versus* −27±25%; p=0.57. Box plots indicate the mean, standard deviation and extreme values.

TABLE 3 Evolution at 6 months of individual and haemodynamic parameters in patients treated with initiation or escalation of immunosuppressive therapy alone

Patient	Sex	Age years	Extrinsic pulmonary artery compression	Increased ^{18}F-FDG uptake in PET scan	Radiological stage	FVC %	WHO/NYHA functional class		6MWD m		mPAP mmHg		Cardiac index L·min^{-1}·m^{-2}		PVR Wood units		Immunosuppressive therapy
							T0	T6	T0	T6	T0	T6	T0	T6	T0	T6	
1	Male	66	Yes (lymph nodes)	Yes	1	96	III	II	490	540	38	29	3.1	3.7	3.2	1.9	Methotrexate
2	Female	40	Yes (lymph nodes)	Yes	1	100	III	II	ND	420	51	29	2.1	2.2	11.7	4.2	Prednisone 60 mg·day^{-1}
3	Female	55	Yes (fibrosing mediastinitis)	Yes	1	42	III	II	190	195	46	30	3.3	2.6	7.4	6.5	Prednisone 60 mg·day^{-1}
4	Male	67	Yes (fibrosing mediastinitis)	No	4	57	II	II	550	530	42	46	2.8	1.9	6.3	10.6	Prednisone 30 mg·day^{-1}
5	Female	58	Yes (fibrosing mediastinitis)	ND	4	40	III	III	390	367	48	39	2.8	2.9	7.3	8.4	Prednisone 30 mg·day^{-1}
6	Female	45	No	ND	4	77	III	III	449	462	39	28	2.8	2.9	6.5	4.8	Prednisone 60 mg·day^{-1}
7	Male	41	No	ND	4	52	II	IV	525	270	39	45	2.3	ND	7.7	ND	Prednisone 60 mg·day^{-1}
8	Male	64	No	ND	2	63	III	III	388	377	42	30	4.3	2.6	4.9	4.7	Prednisone 60 mg·day^{-1}
9	Female	68	No	ND	4	65	III	III	242	ND	44	25	3.3	4.0	7.0	3.6	Azathioprine 100 mg·day^{-1}
10	Female	65	No	ND	4	108	II	III	410	310	48	38	4.1	3.3	6.5	6.6	Prednisone 40 mg·day^{-1}
11	Male	79	No	ND	4	48	III	III	509	ND	56	46	2.3	2.4	9.3	9.5	Prednisone 60 mg·day^{-1}

^{18}F-FDG: ^{18}F-2-fluoro-2-deoxy-D-glucose; PET: positron emission tomography; FVC: forced vital capacity; WHO: World Health Organization; NYHA: New York Heart Association; 6MWD: 6-min walk distance; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; T0: baseline visit; T6: 6-month visit; ND: no data available.

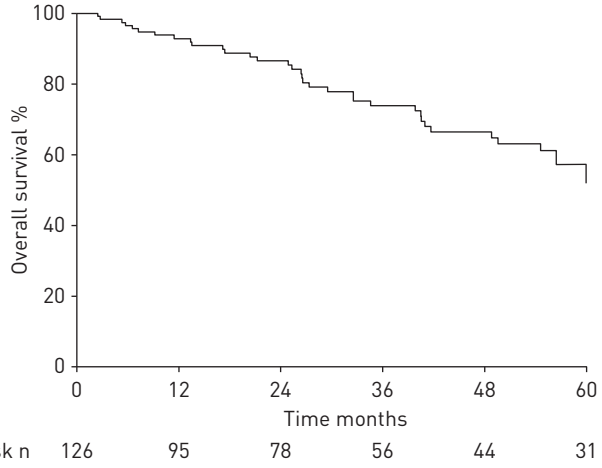

FIGURE 3 Kaplan–Meier analysis of the overall survival in patients with severe sarcoidosis-associated pulmonary hypertension. Survival at 1, 3 and 5 years was 93%, 74% and 55%, respectively.

Safety of PAH-targeted therapy

Safety and tolerability of PAH-targeted medications were similar to what it is observed in patients with PAH. No drug was discontinued due to side-effects. At the time of diagnosis, 68 out of 126 patients (54%) were on long-term oxygen therapy (table 1). At the last follow-up visit, 15 additional patients required long-term supplemental oxygen and 15 patients who were on long-term oxygen therapy at baseline required an increase in oxygen flow rate while on PAH-targeted therapy. The extent of missing arterial blood gas measurements precluded any analysis of the effect of PAH-targeted medications on gas exchange.

Discussion

To the best of our knowledge, this is the largest published series of patients with severe S-APH and the first to report long-term outcomes in these patients. We found that PAH-targeted therapy improved short-term pulmonary haemodynamics without any improvement in exercise capacity. In our cohort, the prognosis was poor, with a 5-year survival rate of 55%. In our series, baseline 6MWD was the only independent predictor of survival.

The median delay between the diagnosis of sarcoidosis and the diagnosis of pulmonary hypertension was >15 years, suggesting that pulmonary hypertension is a complication of advanced sarcoidosis. Accordingly, the vast majority of patients in our study had advanced lung fibrosis, with 72% of patients presenting with radiological stage IV disease at the time of pulmonary hypertension diagnosis and 24% displaying a severe restrictive pattern (FVC <50% predicted). Interestingly, we did not find any correlation between pulmonary haemodynamics and lung function. Moreover, there was no impact of lung function impairment on haemodynamic response to treatment or survival (figure 2).

TABLE 4 Univariate analysis relating survival time to selected baseline variables

	Hazard ratio (95% CI)	p-value
Sex (female)	1.017 (0.573–1.806)	0.954
Age	1.004 (0.977–1.031)	0.794
WHO/NYHA functional class IV	2.010 (1.052–3.840)	0.034
6MWD	0.995 (0.993–0.997)	<0.001
RAP	0.930 (0.861–1.005)	0.066
mPAP	0.997 (0.968–1.027)	0.834
Cardiac index	1.401 (0.994–1.976)	0.054
PVR	0.966 (0.898–1.039)	0.350
FVC	0.984 (0.969–0.999)	0.042
***K*CO**	0.982 (0.968–0.996)	0.013
Radiological stage IV	1.845 (0.954–3.559)	0.069
PAH-targeted therapy	0.845 (0.526–2.650)	0.684

WHO: World Health Organization; NYHA: New York Heart Association; 6MWD: 6-min walk distance; RAP: right atrial pressure; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; FVC: forced vital capacity; *K*CO: transfer coefficient of the lung for carbon monoxide; PAH: pulmonary arterial hypertension.

In our cohort, nine patients were transplanted or died early after pulmonary hypertension diagnosis. In the remaining patients, PAH-targeted therapy improved short-term pulmonary haemodynamics, without significant improvements in exercise capacity. These results are in line with the findings of the only randomised controlled trial with a PAH-targeted medication in patients with S-APH [11]. In that study, 35 patients were randomised to receive either bosentan (n=23) or placebo (n=12). After 16 weeks, bosentan significantly improved pulmonary haemodynamics without any significant change in 6MWD [11]. In contrast, Barnett *et al.* [13] reported an improvement in haemodynamics and 6MWD with different PAH-targeted medications in a retrospective study of 22 patients with S-APH. However, these improvements were seen in only 12 patients, as the most severe patients (n=10) were not reassessed due to death or lung transplantation [13]. Similar results were observed in a recent retrospective study of severe S-APH patients who had significant haemodynamic and clinical improvement on long-term *i.v.* or subcutaneous prostacyclin therapy [14]. Finally, in patients with long-term evaluation of 6MWD (n=50), there was no significant change in exercise capacity, irrespective of their baseline FVC (supplementary table S2), contrary to the findings reported by Barnett *et al.* [13].

The major issue with PAH-targeted therapy in patients with parenchymal lung disease is the potential risk of worsening gas exchange due to ventilation/perfusion mismatch. In a randomised controlled trial of moderate pulmonary hypertension due to chronic obstructive pulmonary disease, a significant worsening in arterial oxygen tension (P_{aO_2}) was observed in patients receiving bosentan when compared with placebo [15]. In the ARTEMIS-IPF study, a double-blind controlled trial of ambrisentan *versus* placebo in patients with idiopathic pulmonary fibrosis, a worsening in lung function and an increased rate of hospitalisations with ambrisentan were reported [16]. In contrast, there was no significant difference in the change in oxygen requirement between the group of patients treated with bosentan and that on placebo in the B-PHIT study where the primary objective was to evaluate the safety and efficacy of bosentan in pulmonary hypertension associated with fibrotic interstitial pneumonias [17]. In a pilot study of the stimulator of soluble guanylate cyclase riociguat in patients with interstitial lung disease-associated pulmonary hypertension, P_{aO_2} decreased by 7±12 mmHg after 12 weeks on therapy [18]. Recently, the phase II study investigating riociguat in patients with pulmonary hypertension associated with idiopathic interstitial pneumonias (ClinicalTrials.gov: NCT02138825) was terminated early due to a possible increased risk for death and other serious adverse events in patients receiving riociguat compared with patients in the placebo group [19]. In the retrospective study of S-APH by Barnett *et al.* [13], 15 out of the 22 patients treated with PAH-targeted therapy required supplemental oxygen after a median follow-up of 11 months. In our study, 30 patients with radiological stage IV sarcoidosis required either long-term supplemental oxygen or an increase in oxygen flow rate while on PAH-targeted therapy. Unfortunately, substantial missing data for arterial blood gas analyses during follow-up precludes us from drawing a definite conclusion on the impact of PAH-targeted therapy on gas exchange in patients with S-APH. At present, there is no evidence to support one type of PAH therapy over another in S-APH. The impact of PAH-targeted therapy on gas exchange should be regularly assessed irrespective of the class of drugs used.

The impact of corticosteroid and immunosuppressive therapy in patients with S-APH is still a matter of debate. In our study, four out of the 11 patients who were treated with immunosuppressive therapy alone improved their short-term pulmonary haemodynamics. It is interesting to highlight that the two patients who had pulmonary hypertension secondary to extrinsic compression of pulmonary arteries by mediastinal lymph nodes responded to immunosuppressive therapy alone. In these patients, ^{18}F-FDG-PET scans revealed metabolically hyperactive mediastinal lymph nodes with an important uptake of ^{18}F-FDG. This suggests that pulmonary hypertension secondary to extrinsic pulmonary artery compression due to an inflammatory process may be reversible. Pulmonary haemodynamics of patients with fibrosing mediastinitis did not improve with immunosuppressive therapy. Therefore, we recommend performing ^{18}F-FDG-PET scans in patients with S-APH with evidence of pulmonary artery compression before considering treatment with immunosuppressive therapy [20]. In the case of pulmonary vascular stenosis from external compression, therapeutic successes were reported with pulmonary vascular angioplasty [21, 22]. This management approach could be discussed in the case of segmental stenosis only. However, the haemodynamic effects and long-term efficacy of these procedures are currently unknown. Venous stenting can be complicated by recurrent stenosis or thrombosis. Two additional patients without any sign of pulmonary artery compression improved with immunosuppressive therapy alone. Despite the absence of ^{18}F-FDG-PET data in these two patients, we can speculate that pulmonary hypertension may have been related to direct granulomatous involvement of the pulmonary vessels. Therefore, even in the absence of extrinsic pulmonary artery compression, a ^{18}F-FDG-PET scan may be helpful to detect patients with S-APH who might respond to immunosuppressive therapy. Patients with S-APH who are corticosteroid-naive might be good candidates for immunosuppressive therapy; however, there is currently

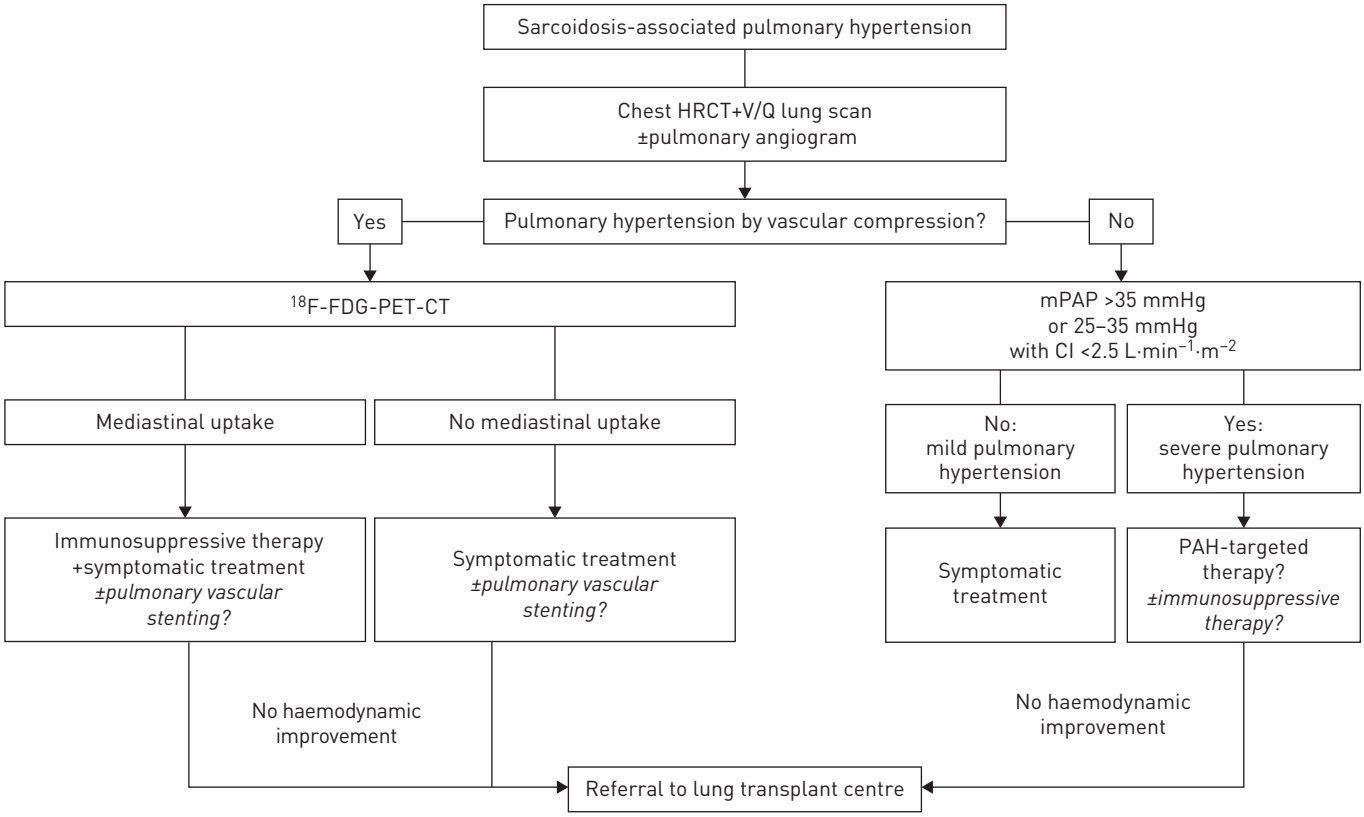

FIGURE 4 Proposed algorithm for the management of sarcoidosis-associated pulmonary hypertension. This algorithm must be read with caution because it relies on retrospective and open-label data, and must therefore be confirmed by future randomised controlled trials. HRCT: high-resolution computed tomography; V/Q: ventilation/perfusion; ^{18}F-FDG: ^{18}F-2-fluoro-2-deoxy-D-glucose; PET: positron emission tomography; mPAP: mean pulmonary artery pressure; CI: cardiac index; PAH: pulmonary arterial hypertension.

no evidence for treating all S-APH patients with immunosuppressive therapy. In all cases, reassessment after 4–6 months on immunosuppressive therapy is essential.

Similar to previous studies of S-APH, we found that overall survival is poor, with 3- and 5-year survival rates of 74% and 55%, respectively [13, 23, 24]. In univariate analysis, age, 6MWD, functional class IV and lung function tests were associated with mortality. In multivariate analysis, however, only 6MWD was a significant predictor of mortality. Interestingly, no haemodynamic variables predicted mortality, although our study included only patients with severe pulmonary hypertension and therefore the prognostic significance of haemodynamic variables in less severe patients cannot be inferred. Despite the poor prognosis of S-APH, only nine patients were referred to lung transplantation during the study. The reasons for this low rate of transplant referral are not apparent from the available data. However, given the poor prognosis of S-APH patients in this study, we recommend that transplantation referral be considered for all potentially eligible patients who do not have clear contraindications. The results allow us to propose a treatment algorithm for severe S-APH (figure 4).

Our results should be interpreted with caution given the methodological limitations inherent to retrospective studies. Lack of follow-up data (particularly gas exchange measurements) was a major limitation. At present, there are no guidelines on the treatment strategy for S-APH, and therefore management strategies rely on clinical experience and a few studies with small numbers of patients. A prospective study of selected S-APH patients, without hypoxaemia and minimal fibrosis, should be performed to properly analyse the effect of PAH-targeted therapies on haemodynamics and exercise capacity. Despite the limitations of this study, we believe that our observations from this large cohort of S-APH may help guide future development of a management algorithm.

In conclusion, our large study of severe S-APH confirms that PAH-targeted therapy improves short-term pulmonary haemodynamics without improving exercise capacity. Corticosteroids or immunosuppressive therapy may improve haemodynamics in selected patients. The long-term survival remains poor, which makes lung transplantation a reasonable option for eligible patients.

Acknowledgements

We thank Laurence Rottat (AP-HP, Hôpital Bicêtre, Le Kremlin-Bicêtre, France) for her hard work in managing the French Pulmonary Hypertension Registry. We also thank Sabrina Zeghmar (Hospices Civils de Lyon, Centre de Référence des Maladies Pulmonaires Rares, Hôpital Louis Pradel, Lyon, France), Stéphanie Polazzi and Anne-Marie Schott (Pôle IMER, Hospices Civils de Lyon, Lyon, France), and all physicians who contributed to the HYPID study. Finally, we thank all physicians from the French Network of Competence Centres for Pulmonary Hypertension (Laurent Bertoletti (Saint-Etienne), Arnaud Bourdin (Montpellier), Matthieu Canuet (Strasbourg), Céline Chabanne (Rennes), Ari Chaouat (Nancy), Claire Dauphin (Clermont-Ferrand), Pascal De Groote (Lille), Nicolas Favrolt (Dijon), Irène Frachon (Brest), Gilbert Habib (Marseille, La Timone), Jocelyn Inamo (Fort-de-France), Sylvie Leroy (Nice), Pascal Magro (Tours), Pierre Mauran (Reims), Patrice Poubeau (Saint-Pierre de La Réunion), Pascal Roblot (Poitiers), Olivier Sanchez (Paris) and François Vincent (Limoges)) and also thank all contributors from the French Competence Centres for Rare Lung Diseases.

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