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Association between Rheumatoid Arthritis and Pulmonary Hypertension: Data from the French Pulmonary Hypertension Registry

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Keywords
Rheumatoid arthritis · Pulmonary hypertension · Connective tissue disease

Abstract
Background: Precapillary pulmonary hypertension (PH), and particularly pulmonary arterial hypertension (PAH), is a life-threatening complication of connective tissue diseases (systemic sclerosis, systemic lupus erythematosus, and mixed connective tissue disease). The relationship between PH and rheumatoid arthritis (RA) has not been clearly established. ***Objectives:*** The aim of the study was to evaluate the relationship between precapillary PH and RA. ***Methods:*** We identified patients with PH and suspected RA included in the French PH Registry between 1 May 2004 and 31 December 2012 and evaluated the prevalence of confirmed RA in this population. RA phenotypes, clinical, functional, and hemodynamic data, and patient outcomes were recorded. ***Results:*** RA was confirmed in 20 patients (70% female; mean age 52 years) with precapillary PH, including 10 patients with PAH, 6 with severe PH due to lung disease, and 4 with chronic thromboembolic PH. The prevalence of RA was 0.35% (95% CI: 0.23–0.54) in the French PH Registry and 0.58% (95% CI: 0.30–1.11) in idiopathic PAH, comparable to that in the general population. The RA phenotype was characterized by the presence of specific RA autoantibodies and joint erosions in 75% of the patients. The outcomes of PH in the RA patients were unremarkable compared to those in other patients from the registry, and RA therapies had no major impact on the cardiopulmonary parameters. ***Conclusion:*** When precapillary PH occurs in RA patients, all PH subsets may be

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identified. The RA prevalence in the French PH Registry is similar to that in the general population, which does not support a specific association or an indication for PH screening in RA patients.

Introduction

Pulmonary hypertension (PH) is defined by a mean pulmonary artery pressure (mPAP) ≥25 mm Hg measured during right-heart catheterization (RHC). A wide range of connective tissue diseases (CTDs) such as systemic sclerosis (SSc), systemic lupus erythematosus, Sjögren syndrome, or antisynthetase syndrome can develop PH, and its occurrence often heralds a worse prognosis [1–9]. The forms of PH found in CTDs are: pulmonary arterial hypertension (PAH) corresponding to a specific vasculopathy of the small pulmonary arteries (group 1 of the PH classification); postcapillary PH due to chronic left heart disease (group 2); PH due to chronic lung disease and/or hypoxia (group 3); and chronic thromboembolic PH (CTEPH) (group 4) [10].

In Western countries, SSc is the most common CTD causing PH. In SSc, the prevalence of PAH ranges from 3.7 to 12% [11–13] and its incidence is 0.61 cases per 100 SSc patient-years [14]. As PAH is a relatively frequent complication of SSc and as early diagnosis may improve survival, yearly screening of these patients for the development of PH is recommended.

Rheumatoid arthritis (RA) has been associated with PH in a few studies, although it is not regarded as a common cause of group 1 PAH [15]. In the Korean REOPARD (Registry of Pulmonary Hypertension Associated with Rheumatic Disease), 8% of the CTD-PH patients were classified as having RA [16]. In the US REVEAL Registry, RA is also reported in 86 out of 2,438 PH patients (3.5%) [17]. There are few prospective studies aimed at determining the prevalence of PH in cohorts of patients with RA. In a series of 144 patients, using a debatable definition based on Doppler echocardiography systolic PAP estimates, a PH prevalence of 31% was suggested [18]. In these patients, the etiological investigation led to the identification of a cardiac or respiratory cause in 33% of the cases. Two other series of 75 and 45 patients using the same methodology have suggested a prevalence of 11 and 27%, respectively [19, 20]. Although strongly limited by the lack of a gold-standard definition of PH (RHC) and the small sample size, these data raise the hypothesis of a link between RA and PH.

The main objective of our study was to investigate a putative association between RA and precapillary PH by comparing the prevalence of RA in the general French population and in the French PH Registry. In addition, we explored the severity and outcome of PAH in patients with RA by comparing its clinical and hemodynamic presentation and outcome to that of other patients with PAH and no RA.

Methods

Patients

Since 2002, the French PH Registry has collected data from patients with precapillary PH (groups 1, 4, 5, and severe PH from group 3 of the PH classification) from the French reference center for severe PH (Hôpital Bicêtre, Université Paris-Sud, Le Kremlin-Bicêtre, France) and 23 regional competence centers [21]. The database was approved by the Commission Nationale de l'Informatique et des Libertés, the organization dedicated to privacy, information technology, and civil rights in France (project #842063). PAH (group 1) was defined as the presence of precapillary PH (mPAP ≥25 mm Hg and pulmonary arterial wedge pressure ≤15 mm Hg) at RHC and the absence of other causes of precapillary PH. Postcapillary PH (mPAP ≥25 mm Hg and pulmonary arterial wedge pressure >15 mm Hg) was not included in the registry. For severe PH due to chronic lung diseases and/or hypoxia, only patients with severe precapillary PH defined by an mPAP >35 mm Hg at rest at RHC were included in the registry. CTEPH was screened by ventilation/perfusion lung scintigraphy and confirmed by helical computed tomography of the chest and/or pulmonary angiography. Patients with postcapillary PH (group 2) were excluded.

We selected patients from the French PH Registry with a suspected history of RA between 1 May 2004 and 31 December 2012. Clinical and hemodynamic data (NYHA [New York Heart Association] functional class, 6-min walk distance, and hemodynamic measurements) were recorded from the registry.

The medical centers at which the patients were followed up were contacted in order to obtain additional data regarding the patients' rheumatic disease. Symptoms of arthritis, the distribution of joint involvement, the duration of symptoms, immunological markers (rheumatoid factor [RF] and/or anti-citrullinated peptide antibody [ACPA], and antinuclear antibodies), radiological signs (the presence of bone erosions that are characteristic of RA according to an analysis by one senior radiologist and one senior rheumatologist), extra-articular manifestations, and disease-modifying antirheumatic drugs (DMARDs; synthetic [sDMARDs] and biologic [bDMARDs]) were recorded from hospital charts. RA was confirmed according to the 1980 American College of Rheumatology criteria.

Any influence of bDMARDs on PH was assessed by comparing the data at 3 time points: (1) at the last assessment before starting treatment with bDMARDs, (2) at the last assessment available during treatment with bDMARDs, and (3) at an intermediate time point.

Statistical Analysis

The statistical analysis was performed using Excel and R software. The results are expressed as a frequency and a percentage for binary variables, and as the mean ± SD or median (range) for con-

tinuous variables according to the normality of the distribution. The two groups were compared using the *t* test or the Mann-Whitney test for quantitative data, and the Fisher exact test for qualitative data. The significance level was set at $p = 0.05$. The Kaplan-Meier method was used for survival analysis; the date of inclusion in the registry was the starting point, and the cutoff date was 31 December 2012. The patients were censored at this date or the date of death.

Results

Subjects

Sixty patients from 20 centers with a history of RA were identified in the registry between 1 May 2004 and 31 December 2012. Data regarding RA were available for 47 of the 60 RA cases. A definite RA diagnosis was confirmed for 20 of these patients. In 12 cases, another diagnosis seemed more likely on the basis of clinical and immunological data (undifferentiated CTD in 7 cases, polymyalgia rheumatica in 2 cases, SSc in 2 cases, and antisynthetase syndrome in 1 case). Fourteen records were incomplete and lacked data to clarify the existence of RA or another CTD.

Among the 20 patients with a definite diagnosis of RA, 10 had been diagnosed with PAH: 8 patients with idiopathic PAH, 1 patient with PAH associated with dexfenfluramine exposure, and 1 patient with portal hypertension. Six patients had PH due to chronic lung disease. High-resolution computed tomography of the chest identified lung fibrosis in 5 patients and nonspecific interstitial pneumonia in 1 case. Four patients had been diagnosed as having CTEPH; none of them had antiphospholipid syndrome. No pulmonary veno-occlusive disease was identified.

Prevalence

By the date of data collection, 5,687 patients had been entered in the registry, of whom 1,375 had idiopathic PAH. These data suggest that the prevalence of RA within this large cohort of 5,687 PH patients and according to the international classification was 0.35% (95% CI: 0.23–0.54), which is similar to the prevalence of RA (estimated at 0.31% [95% CI: 0.18–0.48]) in France in 2001 among the general population. Our data suggest that the prevalence of RA among the 1,375 idiopathic PAH patients in the French PH Registry and according to the international RA classification was 0.58% (95% CI: 0.30–1.11), in accordance with the female predominance observed in PAH (the prevalence of RA among females was 0.51% [95% CI: 0.27–0.82]).

Table 1. Characteristics of the rheumatoid arthritis PH patients ($n = 20$)

Age at diagnosis, years	52±17
Disease duration at the time of inclusion in the PH registry, years	6 (0–38)
Female sex, *n* (%)	14 (70)
Autoantibodies	
Rheumatoid factors and/or ACPA positive, *n* (%)	18 (90)
Rheumatoid factors, % positive	85
UI/mL in positive patients	235±277
ACPA, % positive	82
UI/mL in positive patients	233±236
Antinuclear antibody positive, %	44
X-ray findings, % of patients with at least one erosion	76
Rheumatoid arthritis treatments	
Number of sDMARDS during the whole course of the disease	1 (1–5)
Methotrexate, *n* (%)	15 (75)
Number of patients receiving bDMARDs, *n* (%)	8 (40)
Anti-TNF, *n*	8
Abatacept, *n*	1
Tocilizumab, *n*	1
Rituximab, *n*	1

Results are expressed as the mean ± SD or median (range) unless specified otherwise. ACPA, anti-citrullinated protein antibody; s/bDMARDs, synthetic/biologic disease-modifying antirheumatic drugs; PH, pulmonary hypertension; TNF, tumor necrosis factor.

Characteristics of RA

Among the 20 PH patients with a definite diagnosis of RA, there was a female predominance (70%) and the mean age was 52 ± 17 years. All patients were Caucasian. In the majority of cases (85%), the diagnosis of RA preceded the PH diagnosis by a median of 6 years (0–38). All patients had positive autoantibodies specific for RA (RF in 85% of the cases and/or ACPA in 82% of the cases). Antinuclear antibodies were found in 44% of the cases, but they were all nonspecific according to the usual tests. In 2 patients, secondary Sjögren syndrome was associated with RA. We observed radiological signs of RA in 76% of the cases. All patients but 1 received at least one DMARD. The most frequently used RA treatment was methotrexate (75% of the cases). In 8 patients, the RA activity required the use of bDMARDs; all of them received tumor necrosis factor-α inhibitors (anti-TNF). One patient received abatacept as second-line treatment, followed by tocilizumab. Another received rituximab as second-line therapy (Table 1).

Table 2. Hemodynamic characteristics of the 20 patients with precapillary PH and rheumatoid arthritis

Patient No.	PH classification	Right atrial pressure, mm Hg	Pulmonary arterial pressure, mm Hg	Pulmonary artery wedge pressure, mm Hg	Cardiac output, L × min^{-1}	Cardiac index, L × min^{-1} × m^{-2}	Pulmonary vascular resistance, Wood units	SvO_2, %	Acute vasoreactivity with inhaled NO
1	PAH[a]	28	79	10	3.67	1.6	18.8	42	No
2	PAH	6	47	7	5.57	2.49	7.2	58	No
3	Lung disease	14	56	10	3.9	2	11.8	54	No
4	CTEPH	12	44	15	3.11	1.75	9.3	50	No
5	CTEPH	9	35	11	4.9	2.37	4.9	–	No
6	Lung disease	–	60	7	3	2.08	17.7	60	–
7	PAH	13	38	18[c]	4.13	2.39	4.8	–	No
8	PAH	7	45	13	4.34	3.02	10.4	67	No
9	PAH	3	44	6	1.84	1.26	20.7	54	No
10	PAH	7	27	13	5.01	2.99	2.8	66	–
11	Lung disease	4	37	2	6.15	3.28	5.7	67	No
12	CTEPH	9	44	7	4	2.61	9.3	–	No
13	Lung disease	8	28	12	4.4	2.56	3.6	–	–
14	PAH	0	50	1	4.9	3.13	10.2	–	No
15	Lung disease	11	44	11	5.69	2.8	5.8	–	No
16	PAH	8	40	8	6.33	3.45	5.1	78	No
17	Lung disease	7	46	14	5.21	3.22	6.1	57	No
18	PAH	1	31	5	7.33	3.96	3.5	72	No
19	CTEPH	22	62	13	2	1.22	24.5	47	No
20	PAH[b]	7	40	11	6.35	2.93	4.6	72	No
Median (range)		8 (0–28)	44 (27–79)	10 (1–18)	4.65 (1.84–7.33)	2.70 (1.22–3.96)	6.65 (2.8–24.5)	59 (42–78)	

CTEPH, chronic thromboembolic pulmonary hypertension; NO, nitric oxide; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; SvO_2, mixed venous oxygen saturation. [a] Porto-PH. [b] PAH associated with dexfenfluramine exposure. [c] Diastolic pressure gradient (diastolic pulmonary artery pressure – pulmonary artery wedge pressure) was 10 mm Hg defining mixed pre- and postcapillary PH.

Characteristics of PH

For the whole group of patients with PH and RA, the median (range) right atrial pressure, mPAP, pulmonary arterial wedge pressure, cardiac index (CI), and pulmonary vascular resistance were 8 mm Hg (0–28), 44 mm Hg (27–79), 10 mm Hg (1–18), 2.70 L × min^{-1} × m^{-2} (1.22–3.96), and 6.65 Wood units (2.8–24.5), respectively. A nitric oxide reversibility test was performed on 17 of the 20 patients, and none of them were responders according to the predefined criteria [22]. There was no statistically significant difference in hemodynamic data (mPAP, CI, and total pulmonary resistance) between the various PH subgroups (PAH vs. PH due to lung disease and CTEPH). The individual data are presented in Table 2.

At the time of their inclusion in the registry, 70% of the patients were in NYHA functional class III or IV. The median (range) 6-min walk distance was 235 m (115–403). This test could not be performed with 4 patients due to mobility issues.

Eight of the 10 PAH patients received specific treatment for PAH. During follow-up, 5 patients required sequential combination therapy: 4 needed triple combination therapy (endothelin receptor antagonist [ERA], type 5 phosphodiesterase inhibitors, and prostacyclin analogue) and 1 had double combination therapy (ERA + prostacyclin analogue) to treat PH. Three patients remained on monotherapy (2 with ERA and 1 with type 5 phosphodiesterase inhibitors). Regarding the 4 CTEPH patients, pulmonary endarterectomy was performed on 1 patient – which, however, did not result in significant clinical improvement – and 3 were considered as having distal CTEPH. Five patients were reassessed after the initiation of anti-TNF (n = 4) and rituximab (n = 1), with no detectable clinical or hemodynamic improvement.

Mortality

By 31 December 2012, 7 of the 20 patients had died. The cause of death was directly related to PH in 4 patients (2 refractory right-heart failures and 2 sudden deaths). One patient died from sepsis and 1 from respiratory distress. The cause of death of the last patient could not be

determined. The median duration of follow-up was 32 months (range 1–92). The estimated survival rates at 1 year and 3 years were 84 and 78%, respectively.

Discussion

The main objective of our study was to investigate a putative association between RA and PH. The lowest prevalence of RA in the French PH Registry was 0.35%, which is similar to the one reported for the general French population [23]. This is not in favor of a specific association between RA and PH. Although missing data for some patients with joint involvement might have biased the results, it appears that there is no overrepresentation of patients with RA in the French PH Registry. RA predominantly affects women (sex ratio 4/1) with a peak incidence between 40 and 60 years of age. Our patients with comorbid PH and RA showed similar demographic characteristics to those with RA in France with a 70% female predominance and a median age of 52 ± 17 years at PH diagnosis. It should be noted that all patients were Caucasians. In the majority of cases, the diagnosis of RA preceded the diagnosis of PH with a median delay (range) of 6 years (0–38). Based on these results, one key message is that – contrary to some other rheumatic conditions such as SSc – our data do not support a systematic PH screening program in RA patients.

The RA characteristics did not reveal any specific subphenotype regarding serological markers or structural damage among patients with PH. These patients received a conventional disease-modifying treatment with DMARDs (mostly methotrexate) as first-line treatment according to recommendations. In 40% of the cases, the RA activity required the use of bDMARDs (mostly anti-TNF-α). The fact that bDMARDs were commonly used in our group of patients could be explained by the long duration of RA (10 ± 8 years) and/or by the high activity of the rheumatic disease.

Regarding the PH classification, it is well known that CTDs can be associated with all types of pre- and post-capillary PH, but this had not been reported so far for RA. Among the 20 RA patients with precapillary PH reported on in the present study, one-third had PH due to lung disease and nearly a quarter had CTEPH. In the 4 CTEPH patients, no coagulopathy was identified, especially no antiphospholipid syndrome. In this group of patients, there may be an indirect link between RA and PH. Indeed, it has been established that RA increases the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism), with a relative risk of 2 compared to control subjects [24]. Six patients had PH due to lung disease (group 3 of the PH classification), including 5 patients with lung fibrosis and 1 patient with nonspecific interstitial pneumonia, which represent usual respiratory complications of RA and risk factors for PH (group 3) [25–27]. There are several types of interstitial lung diseases (ILDs) complicating RA: usual interstitial pneumonia, nonspecific interstitial pneumonia, organizing pneumonia, diffuse alveolar damage, respiratory bronchiolitis, desquamative interstitial pneumonia, and lymphoid interstitial pneumonia [28]. Usual interstitial pneumonia is the most frequent one, followed by nonspecific interstitial pneumonia [29]. These pulmonary manifestations are more frequent if ACPAs are present [25]. Dawson et al. [18] have already described similar cases of PH due to ILDs in RA patients. One might also have in mind that sDMARDs (methotrexate) and some bDMARDs (rituximab and TNF-α inhibitors) may also contribute to ILD progression in RA patients [30]. Ten patients had PAH, including 1 case of drug-induced PAH and 1 case of porto-PH. Two cases of drug-induced PAH by leflunomide have previously been described [31, 32]. In our study, no patient received leflunomide. Currently, there is no disease-modifying treatment of RA (DMARDs or bDMARDs) suspected of causing PH [33–35]. Of note, CTDs, and especially SSc, may be associated with pulmonary veno-occlusive disease, a rare and devastating form of PH (group 1′ of the PH classification) [36]. We identified no case of pulmonary veno-occlusive disease among the RA patients.

The estimated survival rates at 1 year and 3 years were 84 and 78%, respectively, in our 20 RA patients with precapillary PH, as compared to a 1-year survival rate of 93% in a Canadian cohort [37]. These survival rates are certainly biased due to the retrospective design of the analysis, with an overrepresentation of prevalent cases of PH [38]. As compared to these findings, in the ItinérAIR-Sclérodermie registry, the 3-year survival rate in SSc-PAH patients was 71% and the 3-year survival rate in SSc-associated PH-ILD patients was 47% [39]. In French patients with systemic lupus erythematosus or mixed CTD, Jaïs et al. [40] reported a 3-year survival rate of 87.2%.

The influence of sDMARDs on PH outcomes could not be evaluated because of insufficient data on the initiation and end dates of treatment. It was possible to assess it in 6 of the 9 patients who received bDMARDs. Regarding the efficacy of anti-TNF therapies, no PH improvement was detected. One patient was treated with rituximab: a woman with seropositive erosive RA and PH

due to pulmonary fibrosis. In this patient, PH improved slightly during the whole period of rituximab therapy. However, she died from sudden death after 43 months of treatment with rituximab. In the literature, there is no described case of RA treated with bDMARDs in the setting of precapillary PH. Castro et al. [41] reported a case of RA with positive RF and secondary Sjögren syndrome who developed PAH 4 years after the diagnosis of RA. The patient did not have disease-modifying treatment at that time. Treatment with azathioprine (200 mg per day) was associated with decreased dyspnea and normalization of estimated PAP (Doppler echocardiography). In our patients, bDMARDs did not seem to influence the evolution of PH apart from preliminary and unclear data from the single patient treated with rituximab.

The main limitation of this study remains its retrospective design from a national registry, which may lead to an underestimation of RA prevalence in this population.

In conclusion, the prevalence of RA in the French PH Registry is similar to the one in the French general population, which tends to disprove any strong association between these two conditions. The consequence is that – conversely to what is recommended for SSc – systematic screening of PH does not seem to be warranted in RA patients. RA therapies did not seem to influence the outcome of PH, although more data are needed on outcomes with biologics.

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