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Etude du rôle pronostique des anticorps anti-U1RNP chez les patients ayant une hypertension artérielle pulmonaire associée aux connectivites

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Table des matières

Résumé

Contexte : L'hypertension artérielle pulmonaire (HTAP) est une complication sévère des connectivites. Le rôle des auto-anticorps en tant que facteurs pronostiques est encore largement méconnu. Cette étude visait à étudier les caractéristiques et la survie des patients souffrant d'HTAP associée aux connectivites et présentant des anticorps anti-U1RNP.

Méthode : Tous les patients avec HTAP associée aux connectivites étaient inclus prospectivement. Les données cliniques, immunologiques et la mortalité étaient ajoutées secondairement à la base de données constituée. Les caractéristiques cliniques et hémodynamiques étaient comparées dans deux groupes constitués selon la présence ou l'absence des anticorps anti-U1RNP. Ces anticorps étaient ensuite analysés en tant que facteurs pronostiques potentiels de survie dans l'HTAP associée aux connectivites, et plus particulièrement la sclérodermie systémique (ScS).

Résultats : 342 patients avec HTAP associée aux connectivites étaient inclus, dont 36 (11 %) avec anticorps anti-U1RNP. Les patients avec anticorps anti-U1RNP étaient plus jeunes au moment du diagnostic d'HTAP et leur tolérance à l'exercice était meilleure que les patients sans ces anticorps. Les paramètres hémodynamiques étaient similaires entre les deux groupes. Parmi les patients avec HTAP associée aux connectivites, la présence d'anticorps anti-U1RNP était un facteur protecteur significatif de mortalité en analyse univariée (HR 0.34 [intervalle de confiance à 95% : 0.18-0.65] ; p<0.001). En analyse multivariée, la présence d'anticorps anti-U1RNP était associée à une meilleure survie (HR 0.44 [IC 95% : 0.20-0.97] ; p=0.043) indépendamment de l'âge, du sexe, des paramètres fonctionnels,

respiratoires et hémodynamiques. Pour l'HTAP associée à la ScS, les résultats étaient similaires mais l'association entre la présence d'anticorps anti-U1RNP et la survie n'atteignait pas la significativité en analyse univariée (HR 0.47 [IC 95% : 0.22-1.02] ; p=0.055) et multivariée (HR 0.47 [IC 95% : 0.20-1.11] ; p=0.085).

Conclusion : La présence d'anticorps anti-U1RNP était associée avec des caractéristiques cliniques différentes des autres patients avec HTAP associée aux connectivites ou à la ScS, mais ne semblait pas influencer les paramètres hémodynamiques. Les analyses de survie suggéraient que la présence d'anticorps anti-U1RNP pouvait être un facteur protecteur de mortalité chez les patients avec HTAP associée aux connectivites ou à la ScS.

INTRODUCTION GENERALE

L'hypertension artérielle pulmonaire (HTAP) est une cause majeure de morbi-mortalité chez les patients souffrant de maladies auto-immunes (aussi appelées connectivites). La sclérodermie systémique (ScS) est la connectivite présentant la prévalence la plus élevée d'HTAP (environ 10%) dont le pronostic est le plus sévère. En effet, la médiane de survie des patients sclérodermiques souffrant d'HTAP se situe autour de 3 ans. Les données sont plus rares concernant la prévalence d'HTAP dans les autres connectivites telles que le lupus érythémateux systémique (LES) ou la connectivite mixte (CM, aussi appelée syndrome de Sharp), mais celle-ci est probablement inférieure. Le pronostic des malades atteints d'HTAP compliquant un LES ou une CM semble meilleur que dans la ScS. Les raisons de cette différence de pronostic ne sont pour le moment que très partiellement comprises.

Les facteurs pronostiques des patients atteints d'HTAP associée à une connectivite les plus étudiés concernent les données hémodynamiques et la tolérance à l'exercice. Il existe peu de données à l'heure actuelle sur la place des auto-anticorps en tant que facteurs pronostiques de survie. Alors que les anticorps les plus fréquemment rencontrés dans la ScS (anticorps anti-centromères, anticorps anti-Scl70) ne semblent pas associés à la mortalité, l'impact de certains anticorps moins fréquents n'a pas été évalué. Parmi ceux-ci, les anticorps anti-U1RNP présentent des caractéristiques intéressantes. En effet, ils sont rencontrés au cours des principales connectivites associées à l'HTAP, mais à des fréquences différentes et sont associées au sein des connectivites à des manifestations différentes. Ainsi, les anticorps anti-U1RNP sont présents chez 2 à 14 % des patients avec ScS, 20 à

40 % des patients avec LES et, par définition, tous les patients avec CM. De plus, il a été suggéré que la présence des anticorps anti-U1RNP pourrait être un facteur prédictif d'atteinte pulmonaire dans le lupus, en particulier d'hypertension pulmonaire. Dans la ScS, bien que les anticorps anti-U1RNP soient classiquement associés avec une maladie moins sévère, plusieurs études ont relevé une association avec l'HTAP.

A notre connaissance, aucune étude ne s'est intéressée au rôle des anticorps anti-U1RNP en tant que facteur pronostique de survie dans l'HTAP des connectivites. Ce travail de Thèse avait donc pour objectifs (i) de comparer les caractéristiques cliniques, fonctionnelles et hémodynamiques des patients avec ou sans anticorps anti-U1RNP ; (ii) d'analyser la survie des patients en étudiant le rôle pronostique des anticorps anti-U1RNP dans l'HTAP des connectivites, et en particulier l'HTAP associée à la ScS.

ABSTRACT

Objectives: Pulmonary arterial hypertension (PAH) is a severe complication of connective tissue diseases (CTDs). This study aimed to study the clinical and hemodynamic characteristics and survival of patients with anti-U1RNP antibodies in CTD-PAH, with a focus on systemic sclerosis (SSc)-PAH.

Methods: We implemented a prospective database that included CTD-PAH patients with clinical, autoantibody and mortality data. We compared the clinical and hemodynamic characteristics accordingly to anti-U1RNP antibodies status. We then assessed whether anti-U1RNP antibodies could be a prognostic factor in CTD-PAH with a focus on SSc-PAH.

Results: A total of 342 CTD-PAH patients were studied, of whom 36 (11%) were anti-U1RNP antibodies positive. Patients with anti-U1RNP antibodies were younger and less functionally impaired than anti-U1RNP negative patients in CTD- and SSc-PAH. Hemodynamic parameters were similar between anti-U1RNP positive and negative patients. In CTD-PAH, anti-U1RNP positivity was negatively associated with mortality in univariable analysis (HR 0.34 [95% CI: 0.18-0.65]; p<0.001). In multivariable analysis, anti-U1RNP was associated with mortality (HR 0.44 [0.20-0.97]; p=0.043), independently of age, sex, functional parameters, lung involvement and hemodynamic. In SSc-PAH, results were similar although the association between anti-U1RNP positivity and survival did not reach significance in univariable

(HR 0.47 [0.22-1.02]; p=0.055) and multivariable analysis (HR 0.47 [0.20-1.11]; p=0.085).

Conclusions: Anti-U1RNP positivity was associated with distinct clinical characteristics and survival in CTD- and SSc-PAH. While hemodynamic parameters were similar between anti-U1RNP positive and negative patients, our results suggest that anti-U1RNP positivity could be a protective factor of mortality in CTD-PAH and SSc-PAH.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a leading cause of morbidity and mortality in patients with connective tissue diseases (CTDs) (1-4). Systemic sclerosis (SSc) is the CTD with the higher prevalence of PAH (around 10%) and the worse prognosis, as a recent meta-analysis estimated the 3-yr overall survival at 56% for patients with SSc and PAH (SSc-PAH) (1,5-7). In other CTDs like systemic lupus erythematosus (SLE) or mixed connective tissue diseases (MCTD), there are less robust data on the PAH prevalence but it is very probably lower than in SSc (3,4). The prognosis of SLE/MCTD-associated PAH (SLE/MCTD-PAH) is also better than in SSc-PAH with a 3-yr overall survival between 74-88% in SLE-PAH and 63-64% in MCTD-PAH (8,9). There is no clear explanation for this difference in survival between CTD-PAH (10,11).

Among the prognosis factors of SSc-PAH, a lot attention has been made on hemodynamics and exercice tolerance (NYHA functional class and 6 min walk test) (12). Data are much more scarce on the role of autoantibodies as prognosis factors in SSc-PAH. Among the few studies assessing this role, anticentromere or antitopoisomerase antibody positivity was not a prognosis factor (1,13). Anti-U1RNP antibodies are another important candidate as prognosis factor in SSc- and CTD-PAH. Anti-U1RNP antibodies are shared by CTDs characterized by different prevalence of PAH and prognosis. Indeed, anti-U1RNP antibodies are found in 2-14% of SSc patients, 20-40% of SLE patients and, by definition, in 100% of MCTD patients (14,15). Some studies have suggested an association between anti-U1RNP

antibodies and the occurrence of pulmonary damage in SLE patients (16) and especially pulmonary hypertension (17-19). In SSc, although anti-U1RNP antibodies are usually associated with a milder disease (15), several studies have suggested an association with PAH (20,21).

Yet, to our knowledge, there are no studies focusing on the role of anti-U1RNP antibodies as prognosis factors in CTD-PAH. This study aimed to fill this gap and study the clinical and hemodynamic characteristics and survival of patients with anti-U1RNP antibodies in CTD-PAH, with a focus on SSc-PAH.

METHODS

I. Cohort of patients and PH diagnosis

The Royal Free Hospital (RFH) Pulmonary Hypertension (PH) database included prospectively all patients who underwent at least one right heart catheterization (RHC) between January 1st 1998 and December 31st 2012. It contains hemodynamic parameters for each RHC: right atrial pressure (RAP), pulmonary capillary wedge pressure (PCWP), mean pulmonary artery pressure (mPAP), mean aortic pressure (mAoP), cardiac index (CI), pulmonary vascular resistances (PVR), arterial oxygen saturation (SaO2) and venous oxygen saturation (SvO2).

According to the guidelines for PH diagnosis (22,23), PH was defined as a mPAP ≥ 25mmHg by RHC at rest without raised cardiac output. Post-capillary PH was defined as PH with a PCWP > 15mmHg. Patients with PH and an elevated PCWP or left ventricular end-diastolic pressure (LVEP) > 15mmHg were considered to have PH secondary to left heart disease (PH-LHD). Patients with pre-capillary PH (PCWP ≤ 15mmHg) were divided into two groups: PH-ILD (PH associated with interstitial lung disease) for patients with a forced vital capacity (FVC) less than 70% predicted and/or ILD extent above 20% on high-resolution CT-scan (HRCT) (24); and PAH (no ILD or ILD with FVC % predicted ≥ 70% and extent on HRCT ≤ 20%).

II. CTD diagnosis

The type of CTD was defined at the time of PH diagnosis. Patients were diagnosed with SSc if they fulfilled the American College of Rheumatology criteria (25) and/or LeRoy and Medsger criteria (26), and classified as having diffuse (dcSSc), limited cutaneous (lcSSc) or limited SSc (lSSc) form according to LeRoy and Medsger (27). SLE were diagnosed according to usual criteria (28,29). In cases of overlap between SSc and SLE, patients were entered into the SSc group. As previously described (30), MCTD was defined in patients without full criteria for a definite CTD and fulfilling at least one of three most commonly used criteria sets of MCTD: Sharp's criteria set, Kasukawa and co-workers or Alarcón-Segovia and Villareal (**Annexe**).

III. Immunological tests

Autoimmune serology was extracted from the clinical database or chart records (data were missing in 31 patients). Identification of ANA specificities (anti-topoisomerase I antibodies (ATA), anti-U1RNP, anti-SSA/Ro, anti-SSB/La and anti-Jo1 antibodies) was performed as part of routine clinical care using both specific immunofluorescence patterns on HEp-2 cells substrate (Bio-Diagnostics Ltd, Upton-upon-Severn, UK) and counter immunoelectrophoresis as previously described (31). Anti-centromere antibody (ACA) was identified by characteristic staining pattern on HEp-2 cell substrate. Anti-double stranded DNA (dsDNA) antibodies were identified by a commercially available ELISA method (Thermo Fisher Scientific, Immunodiagnostics, Uppsala, Sweden).

IV. Other measurements

Other variables were retrospectively implemented into the PH database. Survival data were retrieved from clinical letters or United Kingdom NHS (National Health Service) database (data were censored at 1st March 2013 for analysis). Demographic data, date of disease onset (defined as age at the first non-Raynaud's symptom), pulmonary function tests (FVC % predicted value and DLCO [diffusion capacity of the lung for carbon monoxide] % predicted value), WHO functional class (FC), 6 minute walking distance (6MWD) were retrieved from letters, PH and/or SSc local databases. This study was approved by the Royal Free Hospital local ethics committee (London-Hampstead NRES Reference Number 6398).

V. Statistical analyses

Continuous variables were described using mean and standard deviation (SD) and compared using Kruskal-Wallis test. Categorical variables were described using number and percentage (%) and compared using Fisher exact test. Survival estimates were performed by Kaplan-Meier analyses with comparisons performed by log-rank test.

Multiple Cox proportional hazards regression models examined factors associated with survival. A first non-adjusted model was performed to study survival according to anti-U1RNP positivity. Then two adjusted models were built: (A) model adjusted on age and sex because significant differences were observed between groups; (B) model adjusted on functional parameters, lung involvement (FVC % predicted value, WHO FC) and hemodynamic parameters (RAP, PCWP, mPAP and CI). Proportional hazards hypothesis was verified for each model. Analyses were performed for the entire population of CTD-PAH (SSc-, SLE- and MCTD-PAH) and

then only for SSc-PAH. For the SSc-PAH population, models were also adjusted on the cutaneous subtype (lcSSc vs. dcSSc).

Sensitivity analyses were conducted: (i) because patients with overlap between SSc and SLE were entered into the SSc group, we studied whether exclusion of these patients (n=5) modified results of the Cox regression analyses; (ii) anti-U1RNP status and the type of CTD (SSc, SLE, MCTD) were strongly associated, precluding adjustment on the later (non-convergence of Cox regression models). Consequently we assessed whether adjusting on the type of CTD (SSc, no SSc) with or without excluding MCTD modified the results.

Statistical analyses were performed using R Software version 3.1.2 (32). A p value less than 0.05 was taken as significant throughout.

RESULTS

I. Study population

On 2250 patients who underwent a RHC for a suspicion of pulmonary hypertension, 1013 had been diagnosed previously as having a CTD (SSc, SLE or MCTD). Pulmonary hypertension was confirmed in 626/1013 CTD patients. Among them, 342 CTD patients had pre-capillary PH of group 1 (PAH), and constituted our study population (**Figure 1**).

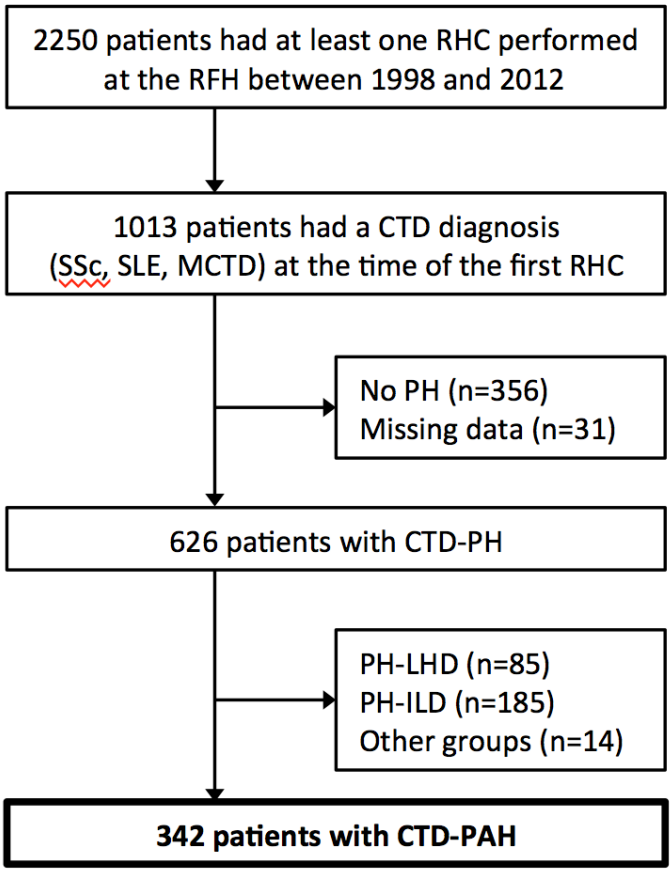


Figure 1: Patients included in this study

As shown in **Figure 2**, the prognosis was significantly different between CTDs. The 3- and 5-year survival rates from PAH diagnosis were 63% and 43% for SSc-, 86% and 85% for SLE-, 100% and 100% for MCTD-PAH, respectively (p<0.001).

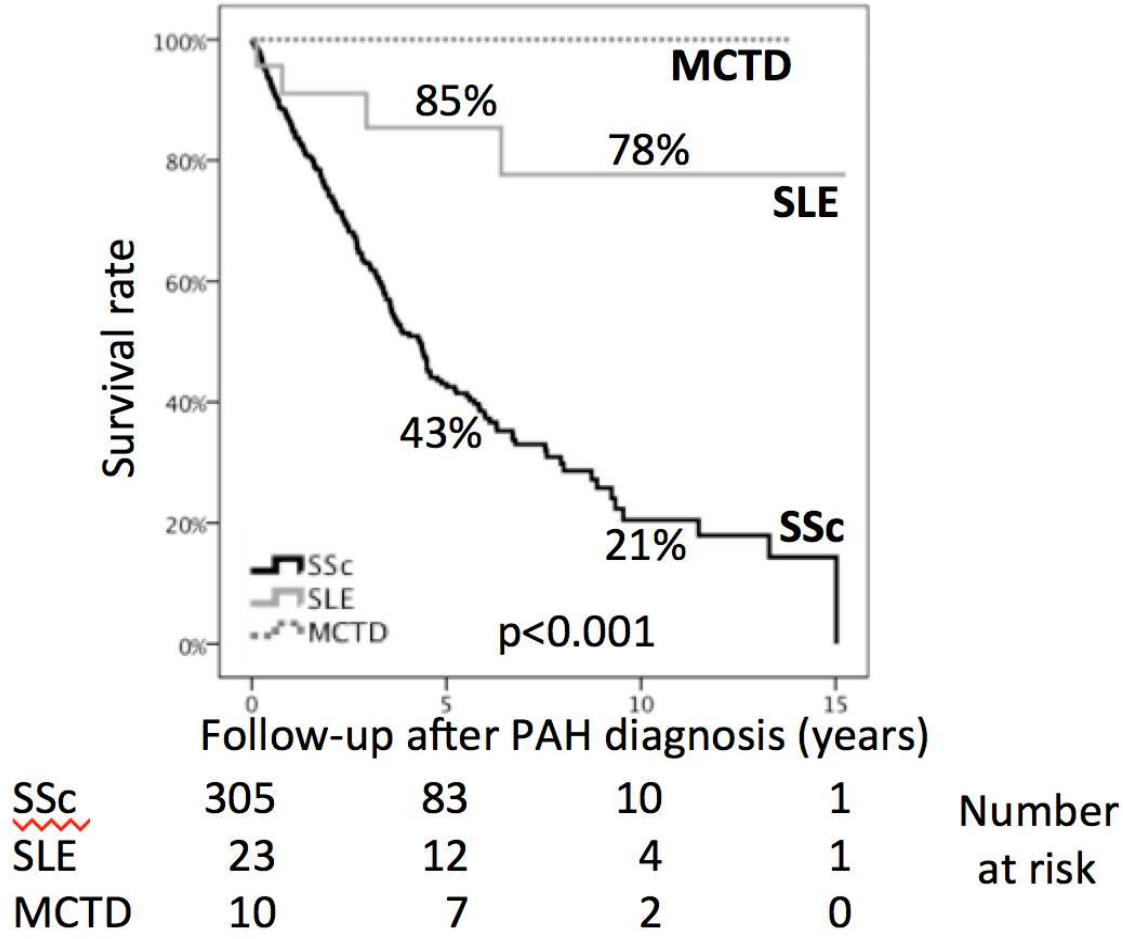


Figure 2. Kaplan-Meier curves of survival after PAH diagnosis

Thirty-six out of 342 (11%) CTD-PAH patients had anti-U1RNP antibodies: 14 with SSc, 10 with SLE, 2 with an overlap SSc/SLE and 10 with MCTD (**Figure 3**).

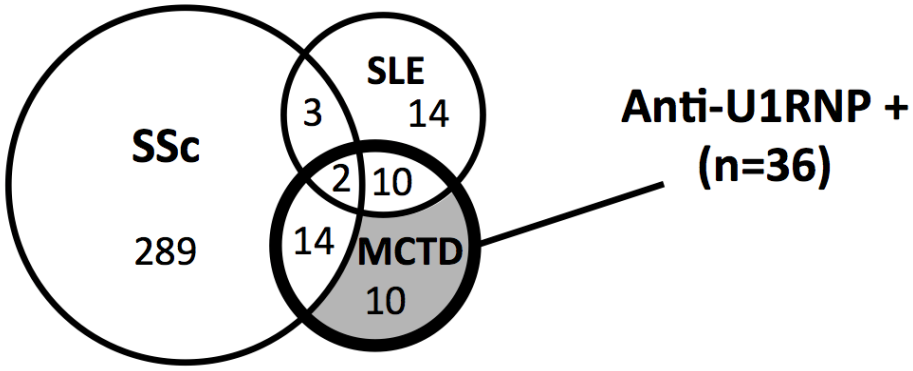


Figure 3. Venn diagram representing distribution of CTDs and anti-U1RNP positivity among the PAH population

II. Anti-U1RNP antibodies in CTD-PAH

A. Clinical and hemodynamic characteristics

Comparisons between anti-U1RNP positive and negative CTD-PAH patients (**Table 1**) showed that anti-U1RNP positive patients were younger (45.3 ± 14.2 versus 61.9 ± 11.8 years; p<0.001) and had a lower CTD duration at PH diagnosis (9.8 ± 8.8 vs. 14.0 ± 10.3 years; p=0.040). Anti-U1RNP positive patients were less functionally impaired as shown by a larger proportion of patients in WHO FC I-II vs. III-IV (39% vs. 22%; p=0.031) and a higher 6MWD (352 ± 109 vs. 258 ± 131 meters; p=0.006). The mean DLCO was higher in the anti-U1RNP positive group (49.1 ± 9.9 vs. 42.6 ± 14.4%; p=0.004). Hemodynamic parameters were similar except for a lower mAoP (94.0 ± 19.9 vs. 101.9 ± 17.8 mmHg; p=0.025) and a higher SaO2 (95.5 ± 2.6 vs. 93.9 ± 4.0%; p=0.020) in the anti-U1RNP positive group.

Table 1. Comparison of clinical and hemodynamic characteristics between anti-U1RNP positive and negative patients

	CTD-PAH				SSc-PAH			
	N	**Anti-U1RNP positive (n=36)**	**Anti-U1RNP negative (n=306)**	**p**	**N**	**Anti-U1RNP positive (n=16)**	**Anti-U1RNP negative (n=292)**	**p**
Age at PH diagnosis, *years*	342	45.3 ± 14.2	61.9 ± 11.8	**< 0.001**	308	54.4 ± 12.8	62.7 ± 11.3	**0.012**
Sex, *female*	342	31 (86)	261 (85)	> 0.999	308	14 (88)	248 (85)	> 0.999
Cutaneous form of SSc, *diffuse*					292	2 (13)	37 (13)	> 0.999
CTD duration at PH diagnosis, *years*	179	9.8 ± 8.8	14.0 ± 10.3	**0.040**	162	11.9 ± 10.6	14.2 ± 10.3	0.386
Follow-up, *years*	338	5.6 ± 4.1	3.7 ± 2.9	**0.010**	305	5.7 ± 4.2	3.6 ± 2.8	**0.032**
FVC, *% predicted*	277	87.8 ± 12.6	93.4 ± 17.8	0.166	255	92.7 ± 13.2	93.4 ± 17.6	0.871
DLCO, *% predicted*	272	49.1 ± 9.9	42.6 ± 14.4	**0.004**	250	48.6 ± 10.9	41.9 ± 13.9	**0.031**
WHO FC I-II	318	13 (39)	62 (22)	**0.031**	286	7 (50)	58 (21)	**0.020**
vs. III-IV		20 (61)	223 (78)			7 (50)	214 (79)	
6MWD, *meters*	92	352 ± 109	258 ± 131	**0.006**	67	321 ± 174	248 ± 130	0.428

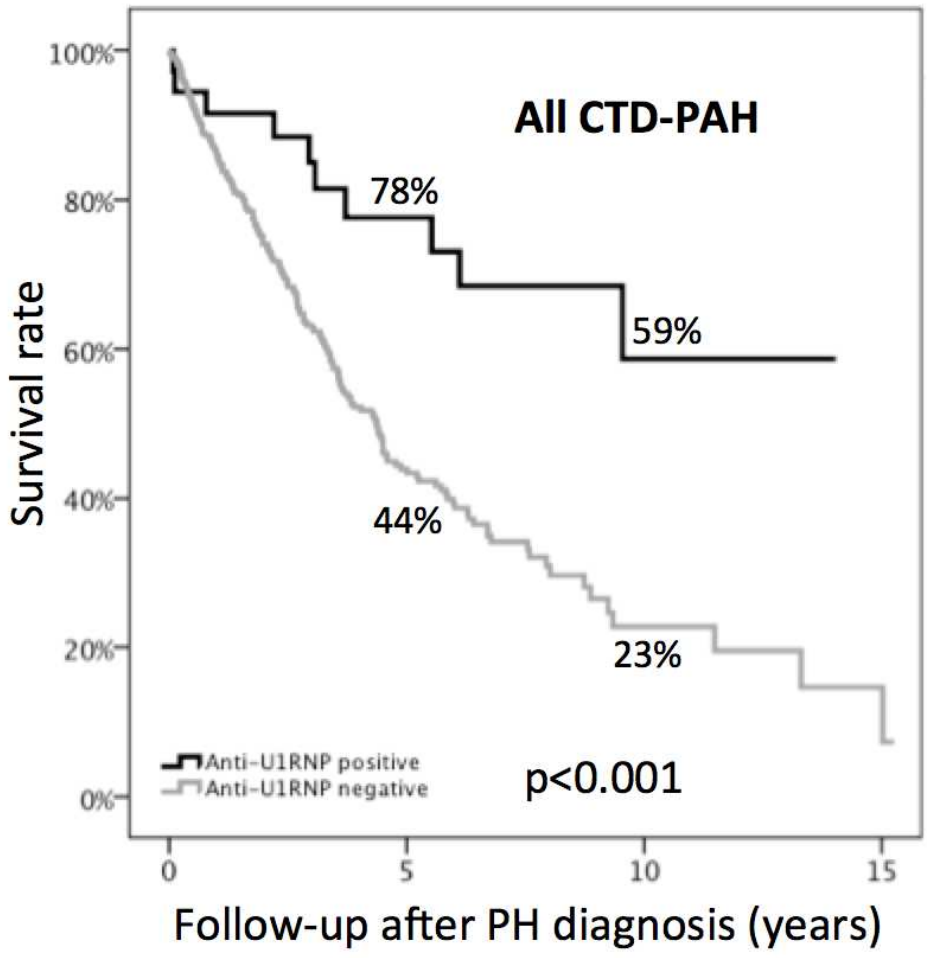
RAP, *mmHg*	338	7.9 ± 6.0	8.1 ± 4.7	0.273	305	7.6 ± 7.2	8.2 ± 4.7	0.088
PCWP, *mmHg*	333	10.0 ± 2.4	10.3 ± 3.3	0.644	302	9.4 ± 2.1	10.2 ± 3.2	0.250
mPAP, *mmHg*	342	39.9 ± 12.2	40.3 ± 12.7	0.889	308	36.8 ± 14.2	39.9 ± 12.4	0.116
mAoP, *mmHg*	301	94.0 ± 19.9	101.9 ± 17.8	**0.025**	270	100 ± 19	102 ± 18	0.606
CI, $L.min^{-1}.m^{-2}$	308	2.6 ± 0.8	2.7 ± 0.7	0.484	277	2.7 ± 1.0	2.7 ± 0.7	0.767
PVR, $dynes.s.cm^{-5}$	323	644 ± 471	615 ± 432	0.584	292	646 ± 640	607 ± 417	0.579
SaO2, *%*	303	95.5 ± 2.6	93.9 ± 4.0	**0.020**	274	95.2 ± 3.4	93.8 ± 4.0	0.134
SvO2, *%*	314	67.7 ± 8.1	65.9 ± 9.9	0.506	283	67.9 ± 8.0	65.8 ± 9.9	0.693

Definition of abbreviations: PH: pulmonary hypertension; CTD: connective tissue disease; FVC: forced vital capacity; DLCO: diffusion capacity of the lung for carbon monoxide; WHO FC: world health organization functional class; 6MWD: 6-minute walking distance; RAP: right atrial pressure; PCWP: pulmonary capillary wedge pressure; mPAP: mean pulmonary arterial pressure; mAoP: mean aortic pressure; CI: cardiac index; PVR: pulmonary vascular resistances; SaO_2: arterial oxygen saturation; SvO_2: mixed venous oxygen saturation

Continuous variables were summarized by the mean ± standard deviation and categorical variables by frequency (percentage).

B. Survival analyses

Kaplan-Meier analysis showed that patients with anti-U1RNP antibodies had a better survival than anti-U1RNP negative patients (**Figure 4**). The 5-year and 10-year survival rates were 78% and 59% in the anti-U1RNP positive group versus 44% and 23% in the anti-U1RNP negative group, respectively (p=0.001).



Anti-U1RNP		Number at risk		
- Positive	36	18	6	0
- Negative	302	84	10	1

Figure 4. Kaplan-Meier curves of survival after PAH diagnosis in all CTD-PAH patients

Cox regression analyses were performed to highlight predictors of mortality in CTD-PAH (**Table 2**). In univariable analysis, anti-U1RNP positivity was associated with a better survival (HR 0.34 [95% CI: 0.18-0.65]; p<0.001). Besides anti-U1RNP positivity, sex, age at PH diagnosis, WHO FC, 6MWD, DLCO % predicted, RAP, PCWP, mPAP, CI, PVR, SaO2 and SVO2 were significantly associated with mortality. There was a trend for a negative association between FVC % predicted and mortality (p=0.054). There was no association between CTD duration at PH diagnosis or mAoP and mortality. In multivariable analysis, anti-U1RNP positivity remained negatively associated with mortality in both models: model A including anti-U1RNP positivity, age at PH diagnosis and sex (HR 0.54 [0.28-1.05]; p=0.067) and model B including anti-U1RNP positivity, age at PH diagnosis, sex, WHO FC, FVC % predicted and hemodynamic parameters (HR 0.44 [0.20-0.97]; p=0.043).

Table 2. Predictors of mortality in CTD-PAH patients

	Univariable	**Multivariable**	
		Model A	**Model B**
Variable	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Sex, *male vs. female*	1.49 (1.03-2.17)*	1.96 (1.33-2.88)***	2.07 (1.31-3.26)**
Age at PH diagnosis, *per year*	1.04 (1.03-1.06)***	1.04 (1.03-1.06)***	1.05 (1.03-1.07)***
CTD duration at PH diagnosis, *per year*	1.00 (0.98-1.02)		
Anti-U1RNP, *positive vs. negative*	0.34 (0.18-0.65)***	0.54 (0.28-1.05)§	0.44 (0.20-0.97)*
FVC, *per %*	0.99 (0.98-1.00)§		0.99 (0.98-1.01)
DLCO, *per %*	0.96 (0.95-0.97)***		
WHO FC, *III-IV vs. I-II*	2.51 (1.65-3.80)***		1.44 (0.86-2.42)
6MWD, *per 100 m*	0.56 (0.41-0.78)***		
RAP, *per mmHg*	1.06 (1.03-1.09)***		1.10 (1.04-1.16)**
PCWP, *per mmHg*	0.91 (0.86-0.95)***		0.85 (0.79-0.92)***
mPAP, *per mmHg*	1.03 (1.02-1.04)***		1.00 (0.98-1.02)
mAoP, *per mmHg*	1.00 (0.99-1.01)		
CI, *per* $L.min^{-1}.m^{-2}$	0.53 (0.42-0.68)***		0.91 (0.64-1.30)
PVR, *per 100* $dynes.s.cm^{-5}$	1.12 (1.09-1.15)***		
SaO2, *per %*	0.91 (0.88-0.94)***		
SvO2, *per %*	0.94 (0.93-0.96)***		0.98 (0.95-1.00)§

§p<0.10, *p<0.05, **p<0.01, ***p<0.001

III. Focus on SSc-PAH

A. Clinical and hemodynamic characteristics

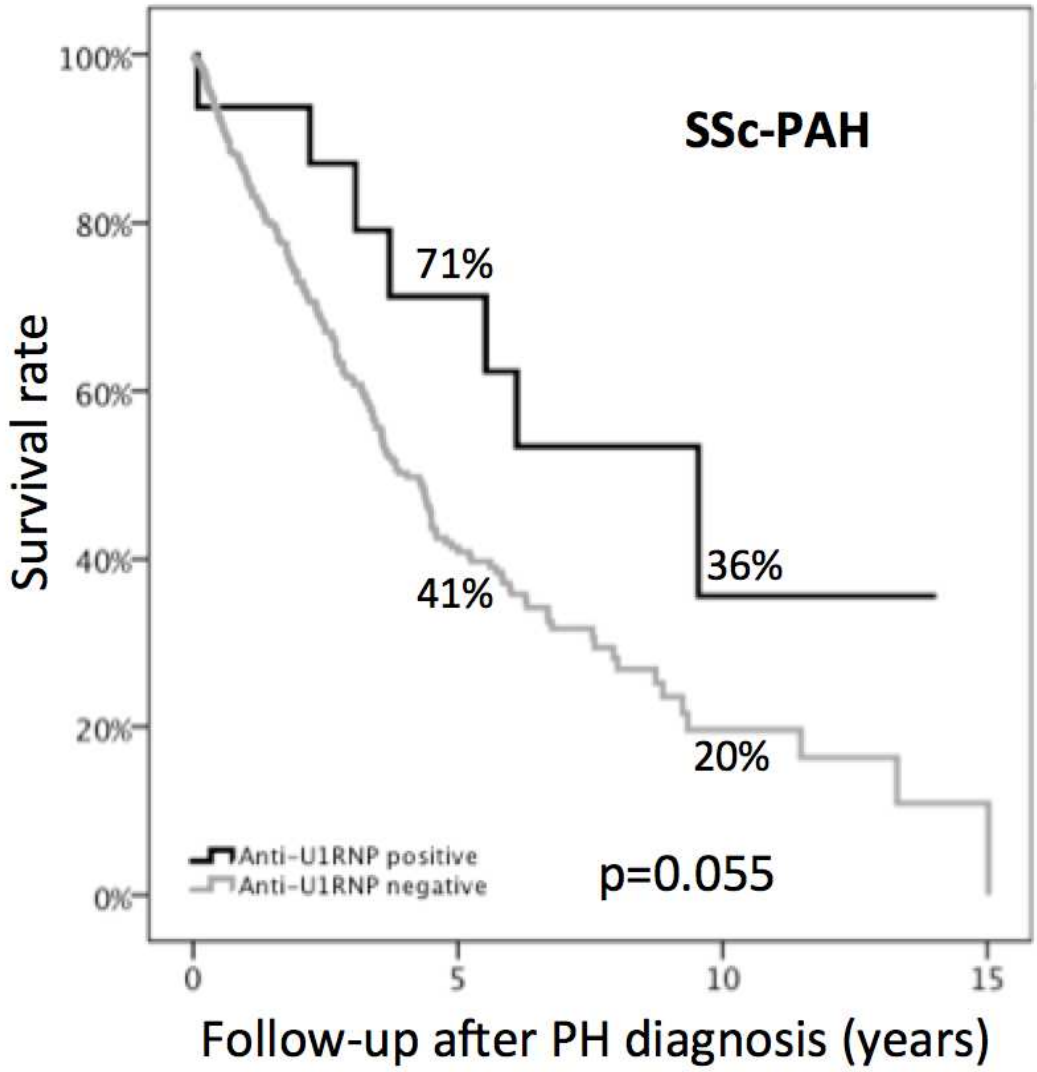
In SSc-PAH, anti-U1RNP positive patients were younger at PAH diagnosis (54.4 ± 12.8 vs. 62.7 ± 11.3 years; p=0.012), had a higher mean DLCO (48.6 ± 10.9 vs. 41.9 ± 13.9 %, p=0.031) and a higher proportion of patients in WHO FC I-II vs. III-IV (50% vs. 21%; p=0.020) than anti-U1RNP negative patients (**Table 1**). There was no difference in the proportion of dcSSc between anti-U1RNP positive and negative patients. Hemodynamic parameters were similar, except for a trend in a lower RAP (7.6 ± 7.2 vs. 8.2 ± 4.7 mmHg; p=0.089) in anti-U1RNP positive patients.

B. Survival analyses

Survival analysis showed a trend for a better survival in anti-U1RNP positive patients (p=0.055; **Figure 5**). The 5-year and 10-year survival rates were 71% and 36% in the anti-U1RNP positive group versus 41% and 20% in the anti-U1RNP negative group, respectively.

Cox regression analyses were performed using a similar methodology than in CTD-PAH (**Table 3**). In univariable analysis, there was a trend towards a positive association between anti-U1RNP positivity and a better survival (HR 0.47 [0.22-1.02]; p=0.055). Besides anti-U1RNP positivity, sex, age at PH diagnosis, WHO FC, 6MWD, FVC % predicted, DLCO % predicted, RAP, PCWP, mPAP, CI, PVR, SaO2 and SVO2 were significantly associated with mortality. CTD duration at PH diagnosis and cutaneous form of SSc were not significantly associated with mortality. In multivariable analysis, anti-U1RNP positivity remained negatively associated with mortality in both models but did not reach significance: model A (HR 0.58 [0.27-1.25];

p=0.164); model B (HR 0.47 [0.20-1.11]; p=0.085).



Anti-U1RNP		Number at risk		
- Positive	16	8	2	0
- Negative	289	75	8	1

Figure 5. Kaplan-Meier curves of survival after PAH diagnosis in SSc-PAH patients

Table 3. Predictors of mortality in SSc-PAH

	Univariable	**Multivariable**	
		Model A	**Model B**
Variable	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Sex, *male vs. female*	1.51 (1.03-2.21)*	1.95 (1.31-2.89)***	1.94 (1.23-3.08)**
Age at PH diagnosis, *per year*	1.03 (1.02-1.05)***	1.04 (1.02-1.05)***	1.04 (1.02-1.06)***
Cutaneous form of SSc, *limited vs. diffuse*	0.72 (0.47-1.12)		
CTD duration at PH diagnosis, *per year*	0.99 (0.97-1.01)		
Anti-U1RNP, *positive vs. negative*	0.47 (0.22-1.02)§	0.58 (0.27-1.25)	0.47 (0.20-1.11)§
FVC, *per %*	0.99 (0.98-1.00)*		0.99 (0.98-1.01)
DLCO, *per %*	0.97 (0.95-0.98)***		
WHO FC, *III-IV vs. I-II*	2.50 (1.64-3.79)***		1.41 (0.84-2.37)
6MWD, *per 100 m*	0.65 (0.46-0.93)*		
RAP, *per mmHg*	1.07 (1.04-1.10)***		1.08 (1.02-1.14)**
PCWP, *per mmHg*	0.91 (0.86-0.96)***		0.86 (0.80-0.93)***
mPAP, *per mmHg*	1.04 (1.02-1.05)***		1.01 (0.99-1.03)
mAoP, *per mmHg*	1.00 (0.99-1.00)		
CI, *per* $L.min^{-1}.m^{-2}$	0.48 (0.37-0.61)***		0.89 (0.62-1.27)
PVR, *per 100* $dynes.s.cm^{-5}$	1.13 (1.10-1.17)***		
SaO2, *per %*	0.92 (0.89-0.95)***		
SvO2, *per %*	0.94 (0.93-0.96)***		0.97 (0.95-1.00)*

§p<0.10, *p<0.05, **p<0.01, ***p<0.001

IV. Sensitivity analyses

Results of the Cox regression analyses in CTD-PAH yielded similar results with the same and constant trend for anti-U1RNP positivity to be associated with a better survival when we reran the models: (i) by excluding SSc/SLE overlap patients (HR for anti-U1RNP positivity in model B: 0.49 [0.22-1.08]; p=0.075); (ii) by adjusting on the type of CTD (SSc vs. non-SSc) (HR 0.52 [0.23-1.15]; p=0.107); (iii) by adjusting on the type of CTD and cutaneous form of SSc (dcSSc vs. lcSSc vs. non-SSc) (HR 0.53 [0.24-1.19]; p=0.124); (iv) by excluding the MCTD patients and adjusting on SSc vs. SLE (HR 0.55 [0.25-1.22]; p=0.140); (v) by excluding the MCTD patients and adjusting on cutaneous form of SSc (dcSSc vs. lcSSc vs. SLE) (HR 0.56 [0.25-1.26]; p=0.160).

DISCUSSION

The main results of our study are as follows: 1) the survival was significantly different between the CTDs (SSc, SLE and MCTD) associated with PAH, in accordance with previous reports, 2) in the population of CTD-PAH, anti-U1RNP positivity was significantly associated with several clinical characteristics and a better survival in univariable and multivariable analysis, and 3) in the population of SSc-PAH, results were similar although the association between anti-U1RNP positivity and survival missed the statistical significance in univariable (p=0.055) and multivariable analysis (p=0.085).

Survival analyses showed that prognosis of SSc-PAH was poor in our population with a 3- and 5-year survival rates were of 63% and 43%, respectively. This is in keeping with the results of a recent meta-analysis of survival studies in SSc-PAH, showing a 3 year-survival of 56% (95% CI: 51-61) (1). Recent data from REVEAL (Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management) showed a 3-year survival in CTD-PAH (SSc represented about 2/3 of the cohort) of 57% and a 5-year survival of 44% (33). Regarding SLE-PAH, we found a 3-year and 5-year survival rates of 86%. This is similar to the 3-year survival of 74% shown in a UK cohort and 88% in a Chinese cohort (8,9). In our study, survival in MCTD-PAH was 100% at 5 years. This result should be interpreted with caution, as only a small number (n=10) of patients were included. However, it confirms that prognosis in MCTD-PAH might be better than SSc-PAH. Chung et al. found a 1-year survival rate of 88% (34) and Condliffe et al. found a 3-year survival

rate of 63% (8) in this population.

Among the characteristics differentiating these CTDs, the positivity of anti-U1RNP antibodies is a major element. Anti-U1RNP antibodies are shared by CTDs characterized by different features: 2-14% of SSc patients, 20-40% of SLE patients and, by definition, in 100% of MCTD patients (14,15). Therefore we first focused on CTD-PAH and compared anti-U1RNP positive vs. negative patients. Patients with anti-U1RNP antibodies were younger and had a lower CTD duration at PH diagnosis. These differences might be due to a higher proportion of SLE or MCTD patients in the anti-U1RNP positive group. Chung et al. showed in the REVEAL cohort that SLE-PAH patients were younger than SSc-PAH (45.5 ± 11.9 vs. 61.8 ± 11.1 years; $p<0.0001$) (34). Condliffe et al. found similar results (42.0 ± 12.9 vs. 63.9 ± 10.5 years; $p<0.001$) (8). These values are comparable to what we found in anti-U1RNP positive and negative groups (45.3 ± 14.2 vs. 61.9 ± 11.8 years; $p<0.001$). In a cohort of 70 Japanese CTD-PAH patients, SLE or MCTD were younger than SSc patients at PH diagnosis. MCTD had the lowest time interval between CTD onset and PH diagnosis (35).

In our study, anti-U1RNP positive patients were less functionally impaired as shown by a higher proportion of patients in WHO FC I or II and a higher 6MWD and had a higher mean DLCO. Again, these differences might be due to a majority of SLE- or MCTD-PAH in the anti-U1RNP positive group. Condliffe et al. showed that SLE-PAH had higher 6MWD and mean DLCO than SSc-PAH, but there was no difference in term of WHO FC (8). Chung et al. found a higher mean DLCO in SLE-PAH than in SSc-PAH. There was no significant difference for 6MWD and WHO FC (34).

Hemodynamic parameters were similar except for a lower mAoP and a higher SaO2 in the anti-U1RNP positive group. In the studies comparing hemodynamic

values between SSc- and SLE-PAH, no differences were found for RAP, mPAP, CI, PVR, SvO2 (8,34,35). Only PCWP was significantly different between SSc- and SLE-PAH in the REVEAL cohort (34). Interestingly, despite a similar hemodynamic severity, anti-U1RNP positive patients had a better survival than those who were negative. Moreover, multivariable analyses showed that anti-U1RNP positivity were associated with survival, independently of age, sex, functional impairment and hemodynamic severity in CTD-PAH. These results highlight a possible serological homogeneity carried by anti-U1RNP antibodies between the different CTD-PAH, with an impact on disease characteristics and survival.

We then assessed whether these findings were similar inside a selected CTD. Among our SSc-PAH population, we found comparable characteristics (younger patients in anti-U1RNP positive group, less functionally impaired with a similar hemodynamic severity). Anti-U1RNP positivity remained associated with a better survival (HR were similar than in CTD-PAH group but did not reach significance). Overall these results are consistent with a unique phenotype and a different prognosis of anti-U1RNP positive patients in CTD- and SSc-PAH.

Anti-U1RNP antibodies bind to U1 small nuclear ribonucleoprotein autoantigen (U1snRNP), a complex that is involved in splicing heterogeneous nuclear RNA into mRNA (15). In SSc, anti-U1RNP antibodies are usually associated with overlap syndromes and are more frequent among lcSSc patients compared to those with dcSSc (36-38). Patients with anti-U1RNP antibodies tend to be younger at SSc diagnosis with a less severe skin involvement and uncommon renal involvement. Puffy hands, Raynaud's phenomenon, arthritis and myositis are commonly seen (15,38,39). Nevertheless, although anti-U1RNP antibodies have been classically associated with a milder disease (15), several studies have suggested an association with PAH in SSc (20,21,40,41). In SLE, anti-U1RNP antibodies, Raynaud’s

phenomenon and antiphospholipid antibodies have been associated with PAH (18,19,42,43). In a cluster analysis of MCTD patients, Szodoray et al. have shown a cluster strongly associated with PH. This cluster presented a higher frequency of swollen hands, Raynaud's phenomenon, livedo reticularis and secondary anti-phospholipid syndrome (44).

The exact mechanisms of PAH in CTD remain elusive. Chow et al. have suggested that anti-U1RNP antibodies in SLE could confer a vasculopathy similar to SSc and that antiphospholipid antibodies could lead to a thromboembolic process (17). Histologic studies of pulmonary arteries in MCTD-PAH patients showed intimal hyperplasia, hypertrophic media, plexiform lesion and locally formed microthrombi. These features are similar to those found in SSc- or SLE-PAH. Vegh et al. found a higher frequence of anti-endothelial cell antibodies and higher serum thrombomodulin and von Willebrand factor antigen concentrations suggesting endothelial cell activation. Interestingly, anti-U1RNP antibodies levels were higher in MCTD patients with PAH than in those without PAH (45). Thus anti-U1RNP antibodies might be a hallmark of a distinct phenotype in CTD-PAH. Greidinger et al. showed that recognition of modified forms of the U1-70-kd autoantigen was associated with different clinical features of rheumatic diseases. They identified an association between oxidatively modified U1-70-kd and Raynaud's phenomenon. The authors suggested that these patients could be at a higher risk of scleroderma-like complications, while patients with high recognition of apoptotically modified U1-70-kd could be at increased risk of lupus-like complications (46).

Previous studies have suggested that immunosuppressive therapy in SLE- or MCTD-PAH could improve survival in responding patients (10,11). Therefore patients with SLE- or MCTD-PAH might have received more frequently an immunosuppressive therapy than SSc-PAH in which this treatment has not proved

efficacy (10). However, one of the results highlighted here is that SSc-PAH patients with anti-U1RNP are different than SSc-PAH patients without anti-U1RNP. Whether or not immunosuppressive treatment could be efficient in SSc-PAH with anti-U1RNP antibodies deserves further studies.

To the best of our knowledge, this study is the first to compare hemodynamic data and survival in a subgroup of CTD-PAH patients characterized by a serological homogeneity. However this work has some limitations. First, this was a single-center study analysing a selected population of patients referred to a PAH referral centre. Nevertheless, we included all consecutive patients with SSc-, SLE- or MCTD-PAH referred to our centre during a 14-year period. This design allows a valuable analysis of the patients' characteristics and outcomes. Moreover, hemodynamic parameters were entered into the database at the time of the RHC resulting in a very limited number of missing data and robustness of hemodynamic variables. Second, due to the retrospective design of clinical variables implementation, we were unable to collect precise data on specific treatment for PAH, especially immunosuppressive therapies. Finally, although this is one of the largest cohorts of CTD-PAH patients, we lacked the statistical power to confirm the association in SSc-PAH patients because of the small number of patients with anti-U1RNP antibodies positive.

In conclusion, our study confirms that survival is significantly different between SSc-, SLE- and MCTD-PAH. Anti-U1RNP antibodies positivity is associated with distinct clinical characteristics and survival in CTD- and SSc-PAH. Although hemodynamic parameters were similar between anti-U1RNP positive and negative patients, anti-U1RNP positivity was negatively and independently associated with mortality in CTD-PAH. In SSc-PAH, survival analyses suggested a negative association between anti-U1RNP antibodies and survival. These results highlight the

clinical need for a better characterization of CTD-PAH phenotypes, especially in therapeutic studies.

CONCLUSION GENERALE

Ce travail de Thèse a confirmé que la survie des patients avec HTAP était différente selon qu'elle s'associait à une ScS, un LES ou une CM. La présence des anticorps anti-U1RNP était associée avec des caractéristiques cliniques et une survie différentes dans l'HTAP associée aux connectivites et en particulier la ScS. Alors que les paramètres hémodynamiques étaient similaires entre les patients avec ou sans anticorps anti-U1RNP, la présence d'anticorps anti-U1RNP était associée avec une meilleure survie dans l'HTAP des connectivites, indépendamment de l'âge, le sexe, les paramètres fonctionnels, respiratoires et hémodynamiques. Dans l'HTAP associée à la ScS, les analyses de survie suggéraient également que les anticorps anti-U1RNP pouvaient être un facteur associé à une meilleure survie, bien que les résultats n'atteignent pas la significativité statistique.

Ces résultats soulignent que l'HTAP n'est pas homogène au sein des connectivites et que la positivité des anticorps anti-U1RNP est associée à un phénotype particulier avec une meilleure survie. Ils soulèvent la question importante de savoir si en miroir de l'homogénéité sérologique, on peut envisager une homogénéité thérapeutique basée non pas sur la connectivite mais sur la positivité des anticorps anti-U1RNP. En effet, les traitements immunosuppresseurs sont potentiellement efficaces au cours des HTAP associées aux LES et aux CM. Il serait intéressant d'évaluer s'ils sont également bénéfiques chez les patients ScS ayant des anticorps anti-U1RNP.

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ANNEXES

Annexe : Classification Criteria for MCTD (adapted from Cappelli et al. (14))

Sharp (1987)	**Kasukawa et al.** (1987)	**Alarcón-Segovia et al.** (1987)
A. Major criteria 1) Myositis, severe 2) Pulmonary involvement a. Diffusion capacity <70% of normal values b. Pulmonary hypertension c. Proliferative vascular lesions on lung biopsy 3) Raynaud's phenomenon or esophageal hypomotility 4) Swollen hands or sclerodactyly 5) Anti ENA ≥1:10,000 and anti-U1snRNP positive and anti-Sm negative B. Minor criteria 1) Alopecia 2) Leukopenia 3) Anemia 4) Pleuritis 5) Pericarditis 6) Arthritis 7) Trigeminal neuropathy 8) Malar rash 9) Thrombocytopenia 10) Mild myositis 11) History of swollen hands	A. Common symptoms 1) Raynaud's phenomenon 2) Swollen fingers or hands B. Anti-U1 snRNP antibody positive C. Mixed symptoms 1. SLE-like findings 1) Polyarthritis 2) Lymphadenopathy 3) Facial erythema 4) Pericarditis or pleuritis 5) Leukopenia (<4000/mm3) or thrombocytopenia (<100,000/mm3) 2. SSc-like findings 1) Sclerodactyly 2) Pulmonary fibrosis, restrictive changes of lung (VC < 80%) or reduced diffusion capacity (DLCO < 70%) 3) Hypomotility or dilatation of esophagus 3. PM-like findings 1) Muscle weakness 2) Elevated serum levels of muscle enzymes (CPK) 3) Myogenic pattern on EMG	A. Serologic Anti-U1 snRNP at a hemagglutination titer of ≥1:1600 B. Clinical 1) Edema in the hands 2) Synovitis 3) Myositis 4) Raynaud's phenomenon 5) Acrosclerosis
At least 4 major criteria plus anti-U1snRNP titer of at least 1:4000 (exclusion criterion: positivity for anti-Sm); or 2 major criteria from among 1, 2, and 3 plus 2 minor criteria plus anti-U1 snRNP titer of at least 1:1000	At least 1 of the 2 common symptoms plus positive for anti-U1 snRNP plus 1 or more of the mixed symptoms in at least 2 of the 3 disease categories	Serologic criterion plus at least 3 clinical criteria, including either synovitis or myositis

AUTEUR : Nom : Sobanski **Prénom : Vincent**

Date de Soutenance : 19 février 2015 à 16h

Titre de la Thèse : Etude du rôle pronostique des anticorps anti-U1RNP chez les patients ayant une hypertension artérielle pulmonaire associée aux connectivites

Thèse - Médecine - Lille 2015

Cadre de classement : Médecine

DES + spécialité : Médecine Interne

Mots-clés : hypertension artérielle pulmonaire – anticorps anti-U1RNP – sclérodermie systémique – lupus érythémateux systémique – connectivite mixte – syndrome de Sharp

Résumé :

Contexte : L'hypertension artérielle pulmonaire (HTAP) est une complication sévère des connectivites. Le rôle des auto-anticorps en tant que facteurs pronostiques est encore largement méconnu. Cette étude visait à étudier les caractéristiques et la survie des patients souffrant d'HTAP associée aux connectivites et présentant des anticorps anti-U1RNP.

Méthode : Tous les patients avec HTAP associée aux connectivites étaient inclus prospectivement. Les données cliniques, immunologiques et la mortalité étaient ajoutées secondairement à la base de données constituée. Les caractéristiques cliniques et hémodynamiques étaient comparées dans deux groupes constitués selon la présence ou l'absence des anticorps anti-U1RNP. Ces anticorps étaient ensuite analysés en tant que facteurs pronostiques potentiels de survie dans l'HTAP associée aux connectivites, et plus particulièrement la sclérodermie systémique (ScS).

Résultats : 342 patients avec HTAP associée aux connectivites étaient inclus, dont 36 (11 %) avec anticorps anti-U1RNP. Les patients avec anticorps anti-U1RNP étaient plus jeunes au moment du diagnostic d'HTAP et leur tolérance à l'exercice était meilleure que les patients sans ces anticorps. Les paramètres hémodynamiques étaient similaires entre les deux groupes. Parmi les patients avec HTAP associée aux connectivites, la présence d'anticorps anti-U1RNP était un facteur protecteur significatif de mortalité en analyse univariée (HR 0.34 [intervalle de confiance à 95% : 0.18-0.65] ; p<0.001). En analyse multivariée, la présence d'anticorps anti-U1RNP était associée à une meilleure survie (HR 0.44 [IC 95% : 0.20-0.97] ; p=0.043) indépendamment de l'âge, du sexe, des paramètres fonctionnels, respiratoires et hémodynamiques. Pour l'HTAP associée à la ScS, les résultats étaient similaires mais l'association entre la présence d'anticorps anti-U1RNP et la survie n'atteignait pas la significativité en analyse univariée (HR 0.47 [IC 95% : 0.22-1.02] ; p=0.055) et multivariée (HR 0.47 [IC 95% : 0.20-1.11] ; p=0.085).

Conclusion : La présence d'anticorps anti-U1RNP était associée avec des caractéristiques cliniques différentes des autres patients avec HTAP associée aux connectivites ou à la ScS, mais ne semblait pas influencer les paramètres hémodynamiques. Les analyses de survie suggéraient que la présence d'anticorps anti-U1RNP pouvait être un facteur protecteur de mortalité chez les patients avec HTAP associée aux connectivites ou à la ScS.

Composition du Jury :

Président : Professeur Pierre-Yves Hatron

Assesseurs : Professeur Eric Hachulla, Professeur Christopher Paul Denton, Docteur John Gerard Coghlan, Professeur David Launay (Directeur de Thèse)