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Phenotypic Profiles Among 72 Caucasian and Afro-Caribbean Patients with Antisynthetase Syndrome Involving Anti-PL7 or Anti-PL12 Autoantibodies

Description of a cohort of 72 patients with anti-PL7 or anti-PL12 antisynthetase syndrome.

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Abstract

Objectives. Antisynthetase syndrome (ASyS) is a rare autoimmune disease. We aimed to determine clinical, biological, radiological, and evolutive profiles of ASyS patients with anti-PL7 or anti-PL12 autoantibodies.

Methods. We performed a retrospective study that included adults with overt positivity for anti-PL7/anti-PL12 autoantibodies and at least one Connors' criterion.

Results. Among 72 patients, 69% were women, 29 had anti-PL7 and 43 anti-PL12 autoantibodies, median age was 60.3 years, and median follow-up period was 52.2 months. At diagnosis, 76% of patients had interstitial lung disease, 61% had arthritis, 39% myositis, 25% Raynaud's phenomenon, 18% mechanic's hands, and 17% had fever. The most frequent pattern on initial chest computed tomography was non-specific interstitial pneumonia and 67% had fibrosis at last follow-up. During follow-up, 12 patients had pericardial effusion (18%), 19 had pulmonary hypertension (29%), 9 (12.5%) had neoplasms, and 14 (19%) died. Sixty-seven patients (93%) received at least one steroid or immunosuppressive drug. Patients with anti-PL12 autoantibodies were younger ($p=0.01$) and more frequently exhibited anti-SSA autoantibodies ($p=0.01$); patients with anti-PL7 autoantibodies had more severe weakness and higher maximum creatine kinase levels ($p=0.03$ and 0.04 , respectively). Initial severe dyspnoea was more common in patients from the West Indies ($p=0.009$), with lower predicted values of forced vital capacity, forced expiratory volume in 1s, and total lung capacity ($p=0.01$, $p=0.02$, $p=0.01$, respectively) contributing to a more severe 'respiratory' initial presentation.

Conclusions. The high mortality and significant numbers of cardiovascular events, neoplasms and lung fibrosis in anti-PL7/12 patients justify close monitoring and question addition of antifibrotic drugs.

Keywords: antisynthetase syndrome; tRNA synthetase autoantibody; idiopathic inflammatory myopathy; anti-PL7 autoantibody; anti-PL12

Highlights

- Anti-PL7 or PL12 antisynthetase syndromes are very rare but very severe diseases
- In our cohort, 20% of patients died during follow-up, 67% had lung fibrosis at last visit and 20% received oxygen
- Repeated screening of lung involvement is required to discuss antifibrotic therapies
- Neoplasms should be screened at diagnosis or during the year after diagnosis
- Pericardial effusion and pulmonary hypertension should be closely monitored

1. Introduction

Antisynthetase syndrome (ASyS), a rare and heterogeneous systemic autoimmune disease, is classified as a subtype of idiopathic inflammatory myopathy (IIM). It is associated with at least one of the following six criteria: interstitial lung disease (ILD), myositis, non-erosive arthritis, Raynaud's phenomenon, mechanic's hands, and unexplained fever. These manifestations are associated with autoantibodies against aminoacyl-transfer RNA synthetase (anti-ARS).

There remains some debate regarding the definition of ASyS. Three main classifications have been suggested: the 2010 Connors' criteria, which included one autoantibody associated with one of the six signs outlined above;¹ the 2011 Solomon criteria, which included one autoantibody associated with two major entities (ILD and myositis) or one major criterion and two minor criteria among arthritis, Raynaud's phenomenon, and mechanic's hands;² and the more recent EULAR/ACR criteria, which are only applicable to patients with ASyS who have anti-Jo1 autoantibodies.³ A recent study by Zanframundo et al. examined the diagnostic performances of the ASyS definitions; the results indicated a need for additional data and consensus-driven classification criteria for ASyS.⁴ An ongoing initiative to better classify ASyS (CLASS) is currently led by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR).⁵

No triggering factors for ASyS have been identified thus far. It has been suggested that damaged cells release aminoacyl-transfer RNA synthetase (ARS); this triggers a complex cascade of both innate and adaptive immune activation, particularly involving anti-ARS autoantibody production, which results in systemic damage.^{6,7} ARS is a cytoplasmic protein synthetase that catalyses the binding of amino acids to their corresponding tRNAs; it contributes to disease pathogenesis via recognition as an autoantigen.⁸ Eight pathogenic autoantibodies have been identified in this syndrome thus far. The most frequently encountered are anti-Jo1 (histidyl) autoantibodies, followed by anti-PL7 (threonyl), anti-PL12 (alanyl), anti-EJ (glycyl), and anti-OJ (isoleucyl) autoantibodies; anti-KS (asparaginyl), anti-Zo (phenylalanyl), and anti-Ha (tyrosyl) autoantibodies are rarely observed.⁹⁻¹⁶ Both anti-PL7 and anti-PL12 autoantibodies are found in 20% of cases of ASyS.¹⁷ Previous studies suggested different clinical presentations according to the type of antisynthetase autoantibody.¹⁸ For example, ILD appears to be more prevalent in patients positive for anti-PL7 and anti-PL12 autoantibodies, compared with patients who have other anti-ARS subtypes; isolated ILD may be the most common presentation in patients with anti-PL12

autoantibodies.^{18,19} Anti-Jo1-negative ASyS patients (including patients positive for anti-PL7 and anti-PL12 autoantibodies) appear to have more severe pulmonary fibrosis and higher mortality rates, compared with anti-Jo1 autoantibody-positive patients.^{20–23} Anti-ARS autoantibodies are not the only autoantibodies found in ASyS. Myositis-associated autoantibodies, such as anti-Sjögren's syndrome-related antigen A (SSA) (Ro52) autoantibody, are reportedly associated with ASyS. A recent study of 60 patients with a diagnosis of ASyS showed that ILD was significantly more prevalent in anti-SSA (Ro52) autoantibody-positive patients, whereas myositis was less prevalent in patients without anti-SSA (Ro52).²⁴

Finally, ILD associated with IIM was encountered more frequently in African/Afro-Caribbean populations, although there were controversies regarding prognostic data in these patients.^{25,26} The present study was performed to determine the clinical, biological, radiological, and evolutive profiles of ASyS patients positive for anti-PL7 or anti-PL12 autoantibodies who were followed up in university hospitals in Bordeaux and Martinique between 2011 and 2021. The secondary objectives were to compare patient profiles according to autoantibody type (anti-PL7 vs. anti-PL12) and place of residence (i.e., Bordeaux in France vs. Martinique in the Caribbean).

2. Materials and Methods

2.1 Study design and patients

This retrospective study was conducted in two different university hospitals in Bordeaux, France, and Martinique in the Caribbean between January 2011 and December 2021. The laboratories of each hospital provided lists of patients positive for anti-PL7 or anti-PL12 autoantibodies between the above dates. Immunologists extracted data from the database during the second quarter of 2022. The date of the first available test providing evidence for any anti-PL7 or anti-PL12 autoantibody was regarded as the date of ASyS diagnosis in this study.

Relevant clinical data were then extracted from medical records, and patients who fulfilled the most used diagnostic criteria (Connors' criteria) were selected. Further selection criteria were adult patients (aged > 18 years) with overt positivity for anti-PL7 or anti-PL12 autoantibodies and at least one of the following criteria: ILD, myositis defined according to Bohan & Peter criteria,²⁷ arthralgia or arthritis, Raynaud's phenomenon, mechanic's hands, and unexplained

persistent fever. Patients were excluded in the event of alternative diagnoses, lack of data, insufficient ASyS criteria in medical records, or refusal to participate in the study.

2.2 Data collection

We extracted data regarding age, sex, smoking status, familial and personal autoimmune history, and any relevant medical data at first visit, diagnosis, during follow-up, and at last visit from each patient's medical file.

Respiratory data included clinical symptoms (dyspnoea with New York Heart Association [NYHA] functional class and cough) and ILD diagnosed on chest computed tomography (CT), with patterns categorised as non-specific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP), organising pneumonia (OP), or lymphoid interstitial pneumonia, according to the American Thoracic Society classification of idiopathic interstitial pneumonia.²⁸ We noted the presence of fibrosis on CT. Pulmonary function tests (PFTs) included diffusing capacity of the lungs for carbon monoxide (DL_{CO}), spirometry, and plethysmography; all variables are shown as the percentage of predicted value (%pred). Pulmonary function was considered altered in patients with forced vital capacity (FVC) < 80%, total lung capacity (TLC) < 80%, and/or DL_{CO} < 80%. Data regarding partial pressure of oxygen (PaO₂) in arterial blood were also collected. Disease progression on PFTs was defined by a decrease in FVC by less than 10% of the predicted value, and/or a reduction in DL_{CO} by less than 15% of the predicted value. Improvement or aggravation on chest CT was determined based on evaluation by the radiologist. Histological findings in bronchoalveolar lavage fluid or surgical lung biopsy were collected if available.

Clinical muscle manifestations (i.e., myalgia, weakness, or dysphagia) were collected. Muscle weakness was defined according to the Medical Research Council (MRC) scale score (0–5) as described previously,²⁹ with MRC score ≤ 3 regarded as severe disease. Electromyography (EMG), muscle magnetic resonance imaging (MRI), and muscle biopsy data were also obtained. Myositis was defined as the presence of symmetrical muscle weakness, elevated creatine kinase (CK) > 180 U/L, myopathic changes on EMG, and overt myositis on muscle biopsy. Myositis was classified as definite (4 criteria met), probable (3 criteria met), or possible (2 criteria met). If suspected (1 criterion met), a diagnosis of myositis was excluded. Muscular changes and improvement/aggravation of IIM were determined on the basis of the physician's evaluation in the medical records.

Arthralgia or arthritis was required to be clinically evident on physical examination for a positive diagnosis. If X-ray arthrography or joint echography was performed, we recorded the

presence of synovitis or degeneration. Raynaud's phenomenon was defined according to the results of physical examination (i.e., colour changes on fingers or toes because of small blood vessel abnormalities); nailfold capillaroscopy descriptions were collected. The mechanic's hands sign was defined as thickened and cracked skin on the fingertips, determined by physical examination. Fever was defined as prolonged temperature $\geq 37.8^{\circ}\text{C}$ for more than 10 days, with no concomitant infection on physical examination and blood tests. Fatigue was also recorded. Furthermore, we recorded other clinical manifestations, including features of dermatomyositis (heliotope rash, Gottron's sign, nailfold bleeding, skin ulcers, and/or vasculitis), gastroesophageal reflux or cardiac involvement with chest pain, troponin/B-type natriuretic peptide levels ($< 10 \text{ ng/mL}$ and $< 50 \text{ pg/mL}$, respectively), pericardial effusion on echocardiography, and/or myocarditis, based on the results of the physician's evaluation. Pulmonary hypertension was considered 'present' if mean pulmonary arterial pressure was $> 25 \text{ mmHg}$ on cardiac catheterisation or 'possible' if pulmonary artery systolic pressure was $> 35 \text{ mmHg}$ on echocardiography. We recorded potential developing overlap syndrome. Sjögren's syndrome was defined by the presence of dry eyes and mouth with positivity for anti-SSA autoantibody and Chilsom 3 or 4 on accessory gland biopsy. We also noted the presence of any associated neoplasms and diagnostic delay with ASyS diagnosis.

Initial biological markers were recorded: lymphocytes ($1500\text{--}4000/\text{mm}^3$), creatinine ($< 100 \mu\text{mol/L}$), lactate dehydrogenase ($140\text{--}245 \text{ U/L}$), C-reactive protein level ($< 5 \text{ mg/L}$), aspartate aminotransferase ($8\text{--}45 \text{ UI/L}$), and alanine aminotransferase ($10\text{--}40 \text{ UI/L}$). Myositis autoantibodies were examined with different generations of dot blot assays (D-TEK, Alphadia), line blot commercial assays (e.g., immunodot EUROIMMUN[®]), or immunoblot strips (EUROLINE[®]) usually called 'dot myositis'. Interpretation of the immunodots was conducted visually and/or using post-scan interpretation software strips; each specific strip was compared with a negative control. Anti-nuclear antibodies (ANA) were detected by indirect immunofluorescence assay on human epithelial type 2 (HEp-2) cells. The positivity cut-off was defined as a titre of $> 1/80$, and the pattern of fluorescence was noted (cytoplasmic, homogenous, nucleolar, or speckled). Anti-SSA (Ro52) autoantibodies were detected on immunodots or with commercial anti-extractable nuclear antigen chemiluminescence or fluorescence enzyme immunoassay.

Treatments received were recorded: steroids, intravenous immunoglobulin, cyclophosphamide, rituximab, azathioprine, methotrexate, mycophenolate mofetil, hydroxychloroquine, or other immunosuppressive treatment, as well as long-term oxygen therapy or lung transplantation. The date of first treatment was noted, along with any dates of

consultation, hospitalisation, intensive care unit admission, last follow-up, or death during follow-up. Relapse was defined as the recurrence of symptoms after remission. Vital status at the end of the recording period was verified by the French death records database (<https://deces.matchid.io>).

2.3 Statistical analysis

Quantitative variables are presented as means (standard deviations) or medians (first and third quartiles) according to their distribution; they were compared using the non-parametric Wilcoxon test. Qualitative data are presented as counts (percentages) and were compared by Fisher's exact test. The Kaplan–Meier method was used to estimate survival. In all analyses, $p < 0.05$ was considered indicative of statistical significance. Data were entered into Excel worksheets, and analyses were performed with STATA (version 17).

2.4 Ethics approval

This retrospective two-centre study received ethical and scientific approval in accordance with French law (IRB 2022/178). Information was sent by either postal letter or delivered by telephone to patients to inform them of the ongoing study and allow them to refuse the review of their medical records. The study was conducted in accordance with the tenets of the Declaration of Helsinki.

3. Results

3.1 Overall patient characteristics

In total, 147 serum samples from 113 patients were screened: 104 in Bordeaux (University Hospital of Bordeaux, UHB) and 43 in Martinique (University Hospital of Martinique, UHM). Finally, 72 patients fulfilling the criteria for ASyS were included in the study (Figure 1).

Patient characteristics according to anti-PL7 or anti-PL12 autoantibody status are summarised in Table 1. The study population included 50 women (69%) and 22 men (31%), with a median age of 60.3 years (49.7–69.3). The median follow-up period was 52.2 months (16.7–95.5). Nine patients (12.5%) had a history of fully controlled autoimmune disease: three with systemic lupus, two with rheumatoid arthritis, and one each with Grave's disease, coeliac disease, Sjögren's syndrome, and systemic scleroderma. The median diagnostic delay

between initial symptom occurrence and the determination of anti-PL7 or anti-PL12 autoantibody positivity was 16.0 months (5.3–47.7). At the first visit, 20 patients (28%) had only 1 of the 6 required criteria, including 13 with ILD, 1 with myositis, 4 with arthritis, and 2 with Raynaud's phenomenon. The first contact with a specialist physician to diagnose ASyS was a consultation in 41 patients (57%) and hospitalisation in 31 patients (43%), including 3 patients who were transferred from the intensive care unit.

3.2 Disease presentation

ILD was identified in 61 patients (87%) during follow-up. The median time between antibody screening test and first chest CT was –4.6 months (–18.3; –0.1). Pulmonary presentations are described in Table 2, along with detailed pulmonary function test results. The most frequent chest CT finding was NSIP, followed by UIP and OP. During follow-up, pulmonary biopsies were performed in 19 patients, which revealed no lesions ($n = 3$), non-classifiable lesions ($n = 10$), NSIP ($n = 2$), UIP ($n = 1$), OP ($n = 2$), or NSIP + OP ($n = 1$). Twenty-seven patients (46%) with pre-existing non-fibrotic ILD or without lung involvement developed lung fibrosis between first and last chest CTs within a median period of 39.1 months (13.6–64.9); lung fibrosis was present in 40 patients (68%) at last follow-up and 13 patients (18%) were receiving long-term oxygen therapy (Table 2).

Thirty-nine patients (54%) had myositis at least once during follow-up: 6 (8%) definite, 12 (17%) probable, and 21 (29%) possible; one patient displayed isolated myositis during follow-up. Fifty-two patients (72%) had myalgia and 34 patients (47%) reported muscle weakness (MRC score < 5/5), among whom 19 (26%) had severe weakness (MRC score ≤ 3). Seven patients (10%) reported dysphagia during follow-up. The CK level was > 180 U/L in 50 patients (71%). EMG was performed in 31 patients, with myopathic abnormalities in 17 (55%). Thirteen patients underwent muscle MRI: 7 patients (54%) had muscle abnormalities consisting of 4 with myositis, 2 with amyotrophy, and 1 with fasciitis. Twelve muscle biopsies (17%) were performed; all showed myositis, but only one showed nuclear actin aggregation.

Sixty-two patients (86%) developed clinically significant arthralgia or arthritis during follow-up. X-ray or ultrasound analyses of painful joints were performed in 33 patients: 15 (45.5%) showed inflammation, 11 (33.3%) had normal findings, and 7 (21.2%) had findings indicative of osteoarthritis. Raynaud's phenomenon was explored by nailfold capillaroscopy in 18 patients: 3 had normal findings and 15 showed a systemic sclerosis-like pattern. Twelve patients (18%) had cardiac involvement: 9 showed pericardial effusion and 3 showed

myocarditis. Notably, the first manifestation of ASyS was cardiac involvement in three patients. Nineteen patients (29%) had suspected pulmonary hypertension on echocardiography during follow-up, which was confirmed by cardiac catheterisation in 12 patients.

Twenty-six patients (36%) had clinical overlap syndrome: 5 lupus, 3 scleroderma, 2 rheumatoid arthritis, 14 Sjögren's syndrome, 2 Hashimoto's thyroiditis, 1 sarcoidosis, and 1 dermatomyositis with anti-MDA5 autoantibody. The median ANA dilution was 1/320, and fluorescence was quasi-exclusively cytoplasmic. Anti-SSA (Ro52) autoantibodies were detected in 41 patients (57%). Patients positive for anti-SSA (Ro52) autoantibodies had a significantly higher rate of fever at diagnosis ($p = 0.04$) with higher C-reactive protein level ($p = 0.04$), higher rate of myalgia during disease evolution ($p = 0.032$), more relapses ($p = 0.029$), and more frequent treatment with rituximab ($p = 0.002$). There were no differences in terms of clinical, radiological, or functional respiratory findings, the frequencies of polymyositis or muscle deficit, and survival rate according to positivity for anti-SSA (Ro52) autoantibodies.

3.3 Associated malignancies

Malignancy was detected in 9 patients (12.5%) at a mean of 5 (–35; 16) months before diagnosis of ASyS: breast cancer in 3 patients, colorectal cancer in 2 patients, and lymphoma, uterine cancer, renal cancer, and lung cancer in 1 patient each. Notably, 7 patients were aged > 50 years, with a median age of 59.2 years (52.6–66.4). The comparison between Caucasian patients (4 cases out of 38 patients over a period of 52 months) and Afro-Caribbean patients (5 cases of 34 patients) with the incidence of cancer over the same period of time in Nouvelle-Aquitaine (Bordeaux) and Martinique yielded an *odds ratio* of cancer of 4.03 and 8.07 respectively.

3.4 Treatment strategies

Patients received specific treatment before diagnosis of ASyS within a median of –20 days (–626; 13). Sixty-six patients (92%) received steroids, including 27 (37.5%) who received high intravenous doses of steroids and 5 who received steroids only. Treatment strategies were too heterogeneous to be clearly summarised. Of note, four patients were treated with tacrolimus: two as anti-rejection treatment, one as salvage therapy with partial response for 1 year followed by relapse, and one also as salvage therapy without efficacy at 3 months; this

patient further received additional baricitinib that led to disease stabilisation. Two patients underwent lung transplantation. In the first patient, transplantation was performed because of rapidly progressive lung disease in 3 months; the patient died of an opportunistic infection 11 months later. The second patient underwent transplantation 7 years after diagnosis because of end-stage lung fibrosis; that patient remained alive at the end of the study. At last follow-up, 18 patients (25%) had no treatment, 8 patients (11%) were receiving prednisone alone, 6 patients (8%) were receiving immunosuppressive drugs alone, and 38 patients (54%) were receiving both prednisone and an immunosuppressive drug (Table 3).

3.5 Comparison between patients with anti-PL7 or anti-PL12 autoantibodies

Patients positive for anti-PL12 autoantibodies were significantly younger than patients positive for anti-PL7 autoantibodies (mean age 55.5 ± 13.1 years vs. 64.3 ± 12.5 years, respectively, $p = 0.01$). There were no significant differences between the two groups during follow-up, based on the initial Connors' criteria (Table 4). At diagnosis, fibrosis was detected in 7 patients (24%) with anti-PL7 autoantibody and 12 patients (29%) with anti-PL12 autoantibody ($p = 0.8$); it was present at last chest CT in 64% and 71% of patients in these two groups, respectively ($p = 0.8$). The patterns did not differ between the two groups. Patients with anti-PL7 autoantibodies had more severe muscle weakness (MRC score ≤ 3 , $p = 0.003$) and higher CK levels ($p = 0.04$, Table 4). Overlap syndrome was significantly more frequent in anti-PL12 autoantibody-positive patients ($p = 0.04$), mainly with Sjögren's syndrome ($p = 0.005$). Moreover, anti-SSA (Ro52) autoantibodies were detected significantly more frequently in patients with anti-PL12 autoantibodies than in patients with anti-PL7 autoantibodies (70% vs. 38%, respectively, $p = 0.01$). There were no differences in neoplasm frequency or probability of survival between the two groups (Figure 2).

3.6 Comparison between patients followed in Bordeaux and Martinique

Anti-PL12 autoantibodies were detected more frequently in Martinique than in Bordeaux ($p = 0.031$). Patients were younger in the Martinique group than in the Bordeaux group (mean age 54.3 ± 13.4 years vs. 63.5 ± 12.9 years, respectively, $p = 0.006$). There were more women in the Martinique cohort ($p = 0.039$). At the first visit, severe dyspnoea (NYHA III or IV) was more common in patients from Martinique than in patients from Bordeaux ($n = 14$ (41%) vs. $n = 5$ (13%), $p = 0.009$). FVC, forced expiratory volume in 1 s (FEV1), and TLC were significantly lower in patients from Martinique than in patients from Bordeaux (58% vs.

73.9%, $p = 0.01$; 62.7% vs. 77.5%, $p = 0.02$; 61.6% vs. 73.2%, $p = 0.01$, respectively). DLCO values did not differ between the two populations. These differences were not statistically significant at the end of follow-up. Fibrotic ILD was present at first chest CT in 12 patients from Martinique (35.3%) and in 7 patients from Bordeaux (18.9%) ($p = 0.2$); it was present at last chest CT in 19 (73.1%) and 21 (63.6%) patients, respectively ($p = 0.6$). There were no differences in ILD prevalence or CT pattern between the two locations. There were also no differences in muscular symptoms between the two sites, except for a higher CK level in patients from Martinique (median maximum CK level 2598 U/L vs. 1136 U/L, respectively, $p = 0.007$). We compared skin lesions (different from Raynaud's phenomenon or mechanics' hands) between the 2 groups of patients, either according to the type of antibody, or the place of life, to look for a difference, especially in patients with anti-PL12 antibodies or patients living in West-Indies and more exposed to UV radiations. We could not find any difference, at most a tendency for more Gottron's sign in Afro-Caribbean patients ($p=0.2$, Supplemental Table 1). Finally, there were no differences in median diagnosis delay, follow-up period, ILD, cancer, treatment, or survival between the two sites (Supplemental Table 2).

4. Discussion

Here, we described a cohort of 72 patients with anti-PL7/12 autoantibodies who were followed up for a median of 52 months. The study population included a larger proportion of women than men. Overall, 87% of patients had ILD and 86% of patients had joint involvement; during follow-up, half of the patients had myositis, Raynaud's phenomenon, or mechanic's hands sign, and one-third of the patients had fever. The median diagnostic delay was 16 months, 12.5% of patients had concomitant neoplasms, and 19% of patients died during follow-up, confirming the severe nature of this disease.³⁰ Patients positive for anti-PL12 autoantibody were younger, whereas patients positive for anti-PL7 autoantibody had more severe muscle weakness (MRC score ≤ 3) and higher maximum CK levels.

4.1 Respiratory and muscular findings

Anti-PL7/12 autoantibodies are suspected to cause ILD in ASyS; in contrast, the most common anti-ARS (anti-Jo1) induces myositis. We found lung involvement in 87% of patients and fibrosis in 68% of patients at the end of follow-up. Our findings regarding the predominance of lung involvement are in agreement with previous observations by Hervier et

al. in a population of 233 ASyS patients divided into three clusters; the cluster with anti-PL7/12 autoantibodies had more lung-restricted disease, whereas clusters with other autoantibodies had higher rates of muscular involvement or more diffuse disease.³⁰ In the present study, the most common pattern on CT was NSIP, followed by UIP and OP. These results were consistent with the findings of Hervier et al.³⁰ but contrary to the findings of Debray et al. in a small series of 13 anti-PL12 autoantibody-positive patients, who predominantly showed NSIP (69%), followed by NSIP + OP (31%).³¹ Although ASyS is classified as a type of idiopathic inflammatory myositis, it is important to consider the high prevalence of ILD. Importantly, the discovery of an ILD in any patient should trigger the screening of ASyS, and, in patients with ASyS, a closer monitoring and/or treatment of a fibrotic evolution. In the present study, 39% and 54% of patients had muscle involvement at the first visit and end of follow-up, respectively; these results differed from the findings of the American and European Network of Antisynthetase Syndrome (AENES) collaborative group, although they reported that 80% of anti-PL7 autoantibody-positive patients had muscle symptoms at last follow-up.¹⁸ Indeed, we found more severe myositis in anti-PL7 patients. Dysphagia has been reported in 15% of ASyS patients,³² which is slightly higher than the rate in the present study and may have been related to the inclusion of anti-Jo1 autoantibody-positive patients in most previous studies. We performed muscle MRI in 13 patients, which revealed muscle abnormalities in 54% of patients and muscular changes on EMG in 55% of patients, consistent with the results reported by Andersson et al.³³; notably, MRI has 80% sensitivity and 82% specificity for myositis.³⁴

4.2 Major cardiac findings

Pericardial effusion or myocarditis and pulmonary hypertension were identified in 18% and 29% of patients, respectively. In two Japanese and French cohorts, pericarditis was frequently associated with anti-PL7/PL12 autoantibodies;^{35–38} it was present in 50% of patients in the EUMYONET cohort.³⁹ Moreover, Hervier et al. reported a significantly lower 3-year survival rate of 58% ($p < 0.001$) for patients with pulmonary hypertension, highlighting the importance of initial and repeated screenings for these cardiovascular manifestations in ASyS during follow-up.⁴⁰ Finally, cardiac MRI could be useful at diagnosis or during follow-up for the diagnosis and treatment of potential myocarditis to prevent ventricular dilatation and/or worsening of systolic dysfunction in patients with ASyS.⁴¹

4.3 Neoplasms

Neoplasms were found in 12.5% of patients, similar to the rate in the EuroMyositis study (12%) reported in 2017,⁴² mainly in patients between 42 and 58 years old. Ebrahimi *et al.* also reported a significantly higher rate of malignancies in patients with anti-PL7 autoantibodies.⁴³ However, one recent meta-analysis identified ASyS as a myositis subtype that was a non-significant factor for cancer, although only 2 studies could be analyzed for this factor, including the EuroMyositis study.⁴⁴ There are no clear recommendations for neoplasm screening in patients with anti-PL7/12 ASyS, compared with other cancer-associated types of myositis, such as anti-transcription intermediary factor 1-gamma (anti-TIF1 γ), anti-NXP2, or anti-hydroxy-3-methylglutaryl-coenzyme A reductase (anti-HMGCR) autoantibodies.⁴⁴ However, the high rate and OR of neoplasms in our cohort, especially in the West Indies, indicates the importance of neoplasm screening, particularly in patients aged > 50 years (Figure 3).

4.4 Overlapping autoimmune diseases

Overlapping autoimmune diseases, mainly Sjögren's syndrome, were detected in 36% of patients, which may have led to the overestimation of lung involvement in our study population. The presence of anti-SSA (Ro52) autoantibodies is associated with IIM and Sjögren's syndrome, such that the incidence of ILD is higher and progress of ILD is more rapid than in patients without anti-SSA autoantibodies.⁴⁵

We found no differences in respiratory findings (clinical, radiological, functional, and evolutive) between patients with and without anti-SSA (Ro52) autoantibodies in our study population.

4.5 Treatment options

There are no standardised recommendations regarding the treatment of ASyS. However, in 2021, Fujisawa *et al.* published a review regarding the management of myositis-associated ILD with some specifications for ASyS,⁴⁶ but not anti-PL7/PL12 autoantibodies. In the present study, steroids were the drugs most frequently prescribed along with immunosuppressive agents; retrospective studies showed that these steroid-sparing agents (i.e., immunosuppressive agents) were effective in 50% to 80% of cases.⁴⁷⁻⁵⁰

Notably, although intravenous cyclophosphamide was administered in half of our patients, there have been no randomised control trials of cyclophosphamide in ASyS patients to

support its use in this manner. Nonetheless, in 2015, Ge et al. reported that 80% of patients with IIM who received cyclophosphamide showed improved strength; moreover, 87.5% of patients showed normalisation of CK levels, and 57.6% and 64.3% showed increases in FVC and DL_{CO}, respectively. Notably, 58% of patients with acute/subacute ILD survived after intravenous cyclophosphamide treatment.⁵¹ Rituximab was used in 25% of patients. In the Rituximab in Myositis (RIM) study, > 80% of patients in the rituximab group achieved remission at 6 months, with significant steroid sparing and a better response in patients with ASyS and IIM.⁵² Andersson et al. reported increases of 24%, 22% and 17% in the median percent predicted FVC, FEV1, and DL_{CO}, respectively, after rituximab treatment.⁵³ Other treatments, such as tacrolimus and baricitinib, were used as salvage therapies. Multiple observational retrospective studies have suggested that anticalcineurin drugs are effective in steroid-refractory ASyS/ILD patients,⁵⁴⁻⁵⁶ and 72% of patients with IIM resistant to steroids or immunosuppressive agents responded to tacrolimus.⁴⁹

Three-quarters of patients required treatment at the end of follow-up, similar to previous findings among patients positive for anti-Jo1 autoantibodies.⁵⁷ Moreover, 18% of patients received long-term oxygen therapy, which was slightly higher than the proportion in the study by Marie et al. involving 15 anti-PL7 autoantibody-positive patients.³⁵ Notably, data regarding antifibrotic drugs were not collected, but these new treatments may be discussed together depending on the fibrotic evolution of ILD.^{58,59}

The mortality rate in our study was 19.4%, which was higher than the rate of 9% reported by Hervier et al.³⁰; however, it confirmed the significantly higher mortality rate in ASyS patients than in the general French population. Hervier et al. also suggested that anti-PL7/12 autoantibody positivity was associated with poor outcomes ($p = 0.01$), as well as severe dyspnoea (NYHA ≥ 3) at diagnosis ($p = 0.003$).³⁰

Accordingly, we propose an algorithmic approach for diagnosis, treatment, and follow-up of patients with anti-PL7 or anti-PL12 antisynthetase syndrome, as shown in Figure 3.

4.6 Comparison between patients with anti-PL7 or anti-PL12 autoantibodies

In our cohort, patients with anti-PL12 autoantibodies were younger than patients with anti-PL7 autoantibodies, as reported previously.^{60,61} The proportion of ASyS patients with ILD has been suggested to vary according to the types of autoantibodies present, because ILD was found in 91% of patients with anti-EJ autoantibodies, 85% of patients with anti-PL12 autoantibodies, 77% of patients with anti-Jo1 autoantibodies, and 62% of patients with anti-PL7 autoantibodies.⁶² We found no differences in ILD frequency, chest CT pattern, or change

in severity between first and last visits when we compared patients positive for anti-PL7 autoantibodies and patients positive for anti-PL12 autoantibodies. Myalgia, myositis, and dysphagia were found at equivalent rates in patients with anti-PL7 or anti-PL12 autoantibodies. Recent studies showed that the rate of myositis was higher in patients with anti-PL7 autoantibodies than in patients with anti-PL12 autoantibodies³²; additionally, patients with anti-PL7 autoantibodies had more severe muscle weakness.⁶³ However, we found that maximum CK levels were significantly higher, and the incidence of severe muscle weakness was increased, in patients with anti-PL7 autoantibodies; these findings confirm that the presence of anti-PL7 autoantibodies leads to more muscle damage and rhabdomyolysis.^{63,26} Our findings also confirmed that anti-SSA (Ro52) autoantibodies were significantly more evidenced in patients with anti-PL12.⁶⁴

4.7 Comparison between patients treated in Bordeaux and Martinique

This study was conducted in two different French centres in Bordeaux and Martinique to identify potential ethnic differences in disease phenotypes. Afro-Caribbean patients were younger and had significantly higher rates of positivity for anti-PL12 autoantibodies than for anti-PL7 autoantibodies; in contrast, anti-PL7 autoantibodies were more common in the Bordeaux centre. These observations confirmed the results of a previous study, which showed that the prevalence of anti-PL12 autoantibodies increased according to proximity to the equator.⁶⁵ Ultraviolet radiation may contribute to the pathogenesis of ASyS, although we found no difference in term of dermatomyositis skin lesions between the living site or the antibody type. Additionally, anti-PL12 autoantibodies were more frequent in Black individuals than in White individuals.²⁶ There is some controversy regarding differences in ILD severity according to ethnicity, which may be explained by socioeconomic status,^{25,26} but these data were not collected in our study. Both hospitals depended on French medical statutes and the patient populations had similar socioeconomic statuses. We found higher CK levels in West Indian patients, which may be explained by the high prevalence of Afro-Caribbean descendants in Martinique.⁶⁶ Indeed, the European Federation of Neurology Societies has proposed defining hyperCKaemia as CK > 1.5-fold above the upper limit of normal; this corresponds to 325 U/L and 504 U/L for non-Black women and men, respectively, and 621 U/L and 1201 U/L for Black women and men, respectively.⁶⁷

4.8 Strengths and limitations

This study had several strengths, including its multi-centre and multi-ethnic nature; the significant number of patients considering the rarity of the disease; and the collection of large amounts of data regarding clinical presentation, imaging, respiratory tests, treatments, and follow-up. However, this study also had some limitations, including its retrospective design, non-standardised patient follow-up, with the use of immunodots from different manufacturers. The definition of ASyS remains controversial; we chose to use Connors' criteria, with the awareness that the lack of validated data may lead to patient misclassification. This issue may be resolved by collaborative efforts of the ACR/EULAR regarding disease classification.⁵

5. Conclusion

ASyS is a rare, severe, and multi-systemic disease, which requires physician awareness. In this French multi-ethnic cohort of 72 patients, we confirmed the severity of this disease, particularly with regard to lung involvement. We also found that cardiovascular events (e.g., pericarditis, myocarditis, and pulmonary hypertension) were common in affected patients; therefore, close monitoring is important after a diagnosis is made, along with screenings for potential neoplasms at diagnosis or during follow-up in subsequent months. We proposed a summarised diagnosis and therapeutic framework to help physicians care for patients with anti-PL7/PL12 ASyS. Clearer classification criteria will facilitate prospective multi-centre studies with standardised collection of data from larger numbers of patients, thus providing greater knowledge and improving the prognosis of this incompletely understood rare disease.

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Figure Legends

Figure 1. Flow chart of the study protocol.

Abbreviations: ASyS, antisynthetase syndrome; n, number; UHB, University Hospital of Bordeaux; UHM, University Hospital of Martinique.

Eighteen patients were excluded because an alternative diagnosis remained: another autoimmune disease (lupus, Sharp syndrome, systemic scleroderma, rheumatoid arthritis, psoriasis, inflammatory idiopathic myositis, and anti-Jo1 antisynthetase autoantibody), other causes of muscle disease (idiopathic cardiomyopathy, Shulman fasciitis, drug-induced myalgia), haematological disease, and infectious diseases (malaria and atypical mycobacterial disease).

Figure 2. Kaplan–Meier survival curve during the study period comparing patients positive for anti-PL7 autoantibodies ($n = 28$) and anti-PL12 autoantibodies ($n = 40$, $p = 0.3$).

Figure 3. Suggested algorithmic approach for diagnosis, treatment, and follow-up of anti-PL7 or anti-PL12 autoantibody-positive ASyS (adapted from Connors et al.,¹ Fujisawa et al.,⁴⁶ Opinc et al.,⁶⁸ and Oddis et al.⁶⁹).

Abbreviations: 6MW, 6-minute walk test; AZA, azathioprine; CK, creatine kinase; CNIs, calcineurin inhibitors; CT, computed tomography; CYC, cyclophosphamide; EKG, electrocardiography; EMG, electromyography; ILD, interstitial lung disease; IV, intravenous; IVHD, intravenous high dose; MMF, mycophenolate mofetil; PFT, pulmonary function test; PSA, prostate-specific antigen; RTX, rituximab; US, ultrasound; yr, years.

TABLES

Table 1. Patient Characteristics According to the Presence of Anti-PL7 or Anti-PL12 Autoantibodies

Variables (n)	Anti-PL7 n = 29		Anti-PL12 n = 43		Total n = 72	
Site (%)						
Bordeaux	20	68.9	18	41.9	38	52.8
Martinique	9	31.0	25	58.1	34	47.2
At diagnosis						
Age (yr) (mean SD)	64.3	12.5	55.6	13.7	59.2	13.8
Female sex (%)	19	65.5	31	72.1	50	69.4
Current or former smoker (%)	9	34.6	16	39.0	25	37.3
Familial autoimmune history (%)	0	0	4	9.3	4	5.6
Personal autoimmune history (%)	3	10.3	6	14.0	9	12.5
Connors' criteria (%)						
ILD	23	79.3	32	74.4	55	76.4
Arthritis/arthralgia	15	51.7	29	67.4	44	61.1
Myositis	13	44.8	15	34.9	28	38.9
Raynaud's phenomenon	8	27.6	10	23.3	18	25.0
Mechanic's hands	7	24.1	6	14.0	13	18.1
Fever	5	17.2	7	16.3	12	16.7
Laboratory tests (mean SD)						
Lymphocyte count (/mm ³)	1566.6	554.4	1666.8	1322.6	1625.8	1072.4
ASAT level (U/L)	90.2	102.4	47.9	47.2	65.3	77.2
ALAT level (U/L)	59.6	56.8	43.6	39.5	50.2	47.7
Creatinine (μmol/L)	67.4	16.8	85.9	59.7	78.2	47.6
CRP level (mg/L)	35.9	36.1	34.0	37.8	34.8	36.8
LDH level (U/L)	593.9	488.4	394.8	280.1	461.2	369.2
ANA dilution (median Q1–Q3)	320	320–640	320	160–640	320	160–640
Anti-SSA (Ro52) (%)	11	37.9	30	69.8	41	56.9
Follow-up period (%)						
Connors' criteria (%)						
ILD	23	79.3	38	92.7	61	87.1
Arthritis/arthralgia	24	82.8	38	88.4	62	86.1
Myositis	17	58.6	22	51.2	39	54.2
Raynaud's phenomenon	14	48.3	19	44.2	33	45.8
Mechanic's hands	12	41.4	17	39.5	29	40.3
Fever	9	31.0	12	27.9	21	29.2
Other findings (%)						
Gastroesophageal reflux	15	51.7	28	65.1	43	59.7
Pulmonary hypertension (n = 66)	5	17.9	14	36.8	19	28.8
Pericardial effusion/myocarditis (n = 67)	3	10.7	9	23.1	12	17.9
Chest pain	5	17.2	7	16.3	12	16.7
Overlap syndrome	6	20.7	20	46.5	26	36.1
Sjögren's syndrome	1	3.4	13	30.2	14	19.4
Neoplasm	6	20.7	3	7.0	9	12.5
Death (%)	6	20.7	8	18.6	14	19.4
Delays, median (Q1–Q3) (months)						
Follow-up period	26.0	15.7–75.9	58.2	25.2–96.8	52.2	16.7–95.5
Diagnosis delay	17.2	5.0–40.5	14.6	5.4–63.1	16.0	5.3–47.7
Period between first symptoms and death	96.6	46.1–197.8	97.2	31.4– 272.3	97.2	46.1–197.8
Period between diagnosis and death	23.2	14.3–45.0	49.4	13.5–78.0	27.6	14.3–49.4
ICU admission during follow-up (%)	5	17.2	11	25.6	16	22.2

Abbreviations: ALAT, alanine aminotransferase; ANA, anti-nuclear antibody; ASAT, aspartate aminotransferase; CK, creatine kinase; CRP, C-reactive protein; ICU, intensive care unit; ILD, interstitial lung disease; LDH, lactate dehydrogenase; n, number; Q1, first quartile; Q3, third quartile; SD, standard deviation; yr, years.

Table 2. Respiratory Outcomes According to the Presence of Anti-PL7 or Anti-PL12 Autoantibodies

	Anti-PL7 <i>n</i> = 29		Anti-PL12 <i>n</i> = 43		Total <i>n</i> = 72	
At diagnosis						
Cough (%)	22	75.9	31	72.1	53	73.6
Dyspnoea (%)	25	86.2	36	83.7	61	84.7
Severe dyspnoea (NYHA \geq 3) (%)	8	27.6	11	25.6	19	26.4
First chest CT pattern available (%) <i>n</i> = 71						
NSIP	12	41.4	17	40.5	29	40.8
Undetermined pattern	7	24.1	15	35.7	22	31.0
No ILD	7	24.1	6	14.3	13	18.3
UIP	2	6.9	2	4.8	4	5.6
OP	1	3.4	2	4.8	3	4.2
Fibrosis (CT chest and/or biopsy) (%) <i>n</i> = 71	7	24.1	12	28.6	19	26.8
First PFT available %pred (mean, SD)						
DL _{CO} (<i>n</i> = 41)	44.5	22.3	54.5	18.4	50.6	20.4
FEV1 (<i>n</i> = 58)	74.6	27.2	68.2	21.3	71.1	24.1
FVC (<i>n</i> = 56)	69.1	24.6	65.4	18.9	67.1	21.5
TLC (<i>n</i> = 51)	72.5	23.9	65.4	20.1	68.4	21.9
PaO ₂ (mmHg) (mean, SD) (<i>n</i> = 44)	86.5	11.8	80.4	17.9	83.1	15.7
6-minute walk test (m) (mean, SD) (<i>n</i> = 36)	362.4	88.6	354.6	90.4	357.6	88.5
At the end of follow-up						
Duration of follow-up (median, Q1–Q3, months)	26	15.7–75.9	58.2	25.2–96.8	52.2	16.7–95.5
Dyspnoea (%) <i>n</i> = 67	21	72.4	33	86.8	54	80.6
Severe dyspnoea (NYHA \geq 3) (%) <i>n</i> = 67	9	31.0	7	18.4	16	23.9
Last chest CT pattern available (%) <i>n</i> = 59						
Undetermined pattern	12	48.0	22	64.7	34	57.6
NSIP	6	24.0	8	23.5	14	23.7
UIP	4	16.0	2	5.9	6	10.2
No ILD	2	8.0	2	5.9	4	6.8
OP	1	4.0	0	0.0	1	1.7
Fibrosis (CT chest) (%) <i>n</i> = 59	16	64.0	24	70.6	40	67.8
Long-term oxygen therapy (%)	5	17.2	8	18.6	13	18.1
Last PFT available %pred (mean, SD)						
DL _{CO} (<i>n</i> = 34)	50.7	13.4	45.8	17.9	47.8	16.1
FEV1 (<i>n</i> = 50)	77.1	27.0	77.4	20.3	77.2	23.1
FVC (<i>n</i> = 52)	78.3	25.7	75.6	20.4	76.7	22.5
TLC (<i>n</i> = 43)	74.8	25.9	66.9	13.4	69.8	19.1
PaO ₂ (mmHg) (mean SD) (<i>n</i> = 30)	85.4	14.3	80.1	14.4	82.4	14.4
6MW (m) (mean SD) (<i>n</i> = 27)	352.7	128.8	365.4	122.4	360.7	122.5

Abbreviations: 6MW, 6-minute walk test; CT, computed tomography; DLCO, diffusing capacity of the lungs for carbon monoxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; ILD, interstitial lung disease; m, metres; n, number; NSIP, non-specific interstitial pneumonia; NYHA, New York Heart Association; OP, organising pneumonia; PaO₂, partial pressure of oxygen; PFT, pulmonary function test (by percentage of predicted value [%pred]); Q1, first quartile; Q3, third quartile; SD, standard deviation; TLC, total lung capacity; UIP, usual interstitial pneumonia.

Table 3. Treatment Received and Disease Evolution During Follow-Up According to the Presence of Anti-PL7 or Anti-PL12 Autoantibodies

	Anti-PL7 <i>n</i> = 29		Anti-PL12 <i>n</i> = 43		Total <i>n</i> = 72	
Total number of treated patients (%)	28	96.6	39	90.7	67	93.1
Steroids (%)	28	96.6	38	88.4	66	91.7
HDIV prednisone	10	34.5	17	39.5	27	37.5
Mycophenolate mofetil (%)	15	51.7	23	53.5	38	52.8
Cyclophosphamide (%)	15	51.7	20	46.5	35	48.6
Hydroxychloroquine (%)	6	20.7	16	37.2	22	30.6
Rituximab (%)	4	13.8	14	33.3	18	25.4
Methotrexate (%)	6	20.7	11	25.6	17	23.6
Azathioprine (%)	5	17.2	10	23.3	15	20.8
Long-term oxygen therapy (%)	5	17.2	8	18.6	13	18.1
IVIg (%)	2	6.9	4	9.3	6	8.3
Other immunosuppressive agents (%)	1	3.5	4	9.3	5	6.9
Lung transplantation (%)	0	0.0	2	4.7	2	2.8
Evolution (%)						
Relapse	12	41.4	18	41.9	30	41.7
Pulmonary evolution						
Stable	10	34.5	10	23.3	20	27.8
Worsening	6	20.7	12	27.9	18	22.5
Improvement	6	20.7	10	23.3	16	22.2
Not applicable	7	24.1	11	25.6	18	25.0
Muscular evolution						
Stable	0	0.0	4	9.3	4	5.6
Worsening	4	13.8	3	7.0	7	9.7
Improvement	10	34.5	6	14.0	16	22.2
Appearing during follow-up	3	10.3	7	16.3	10	13.9
Not applicable	12	41.4	23	53.5	35	48.6

Abbreviations: HDIV, high dose intravenous; IVIg, intravenous immunoglobulin; *n*, number.

Table 4. Comparison of Patients with Anti-PL7 or Anti-PL12 Autoantibodies

Variable (n)	Anti-PL7 29		Anti-PL12 43		p-value
Age (yr) (mean SD)	64.3	12.6	55.5	13.8	0.014
Female sex (%)	19	65.5	31	72.1	0.608
<u>Connors' criteria</u>					
ILD	23	79.3	38	92.7	0.148
Arthritis/arthritis	24	82.8	38	88.4	0.510
Myositis	17	58.6	22	51.2	0.632
Raynaud's phenomenon	14	48.3	19	44.2	0.811
Mechanic's hands	12	41.4	17	39.5	1.000
Fever	9	31.0	12	27.9	0.797
Myalgia (n, %)	21	72.4	31	72.1	1.000
Myositis (n, %)	17	58.6	22	51.2	0.632
Severe weakness (MRC score ≤ 3) (n, %)	12	41.4	7	16.3	0.028
Dysphagia (n, %)	4	13.8	3	7.1	0.433
Myopathic changes at EMG (n, %) (n = 31)	10	62.5	7	46.7	0.479
Muscular abnormalities at MRI (n, %) (n = 13)	3	42.9	4	66.7	0.592
Maximum CK level (mean SD)	2902.6	4113.7	1107.6	1837.4	0.043
Dyspnoea at first visit (%)	25	86.2	36	83.7	1.000
Fibrosis evolution (%)	11	44.0	16	47.1	1.000
Pulmonary hypertension (n = 66)	5	17.9	14	36.8	0.108
Pericardial effusion/myocarditis (n = 67)	3	10.7	9	23.1	0.333
Neoplasm	6	20.7	3	6.9	0.144
Anti-SSA (Ro52)	11	37.9	30	69.8	0.015
ICU admission during follow-up (%)	5	17.2	11	25.6	0.565
Death (%)	6	20.7	8	18.6	1.000

Abbreviations: n, number; SD, standard deviation; yr, years; ILD, interstitial lung disease, MRC score, Medical Research Council 5-point scale score (0–5); EMG, electromyography; MRI, magnetic resonance imaging; CK, creatine kinase; ICU, intensive care unit.

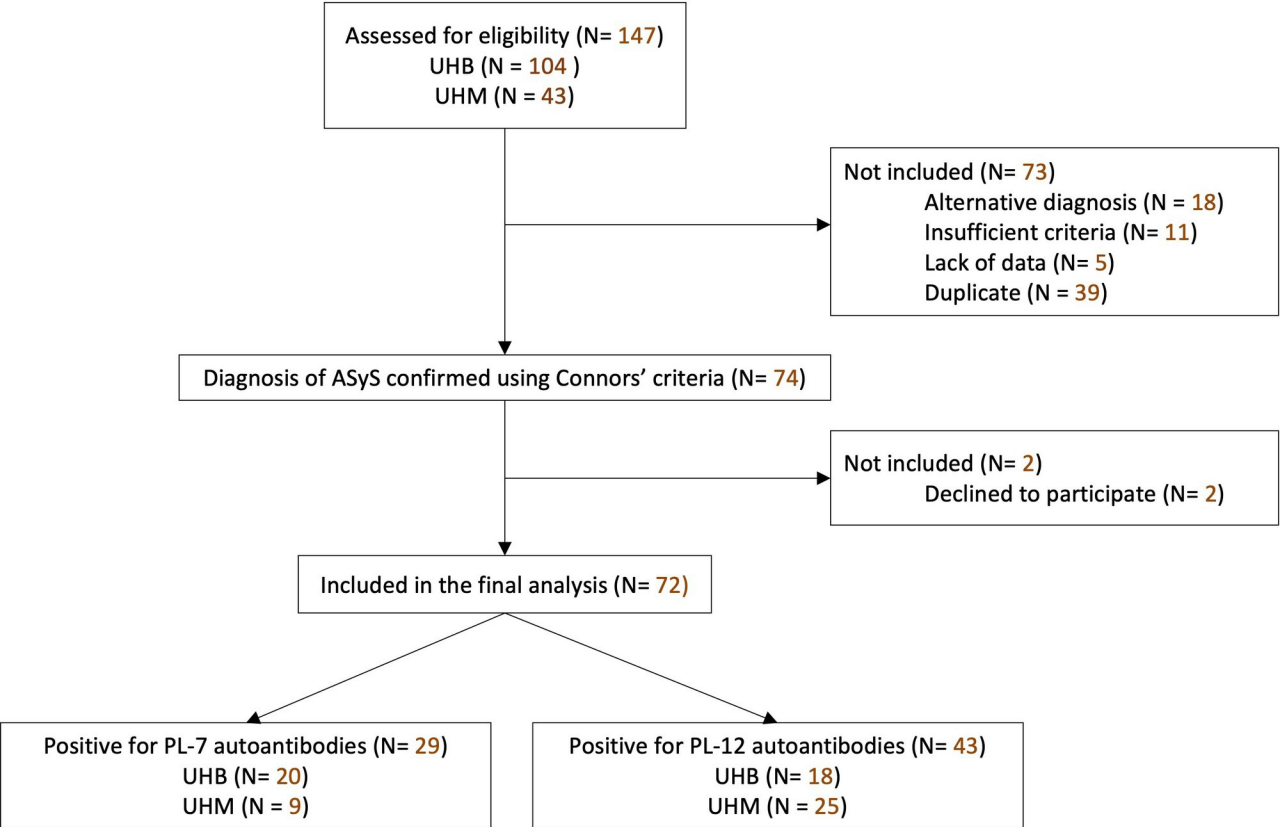
Supplemental Table 1. Comparison of Patients' Skin Characteristics Between Patients From Bordeaux (Caucasians) and Martinique (Afro-Caribbean), and According to the Presence of Anti-PL7 or Anti-PL12 Autoantibodies.

	Antibody		Total	<i>p</i>
	Anti-PL7	Anti-PL12		
N	29	43	72	
≥ 1 DM manifestation	12 60.0%	17 53.1%	29 55.8%	0.776
Gottron's sign	7 35.0%	9 28.1%	16 30.8%	0.759
Heliotrope rash	6 30.0%	9 28.1%	15 28.8%	1.000
Nail pain (manicure sign)	5 25.0%	6 18.8%	11 21.2%	0.730
Shawl sign	6 30.0%	5 15.6%	11 21.2%	0.299
Photo-sensibility	5 25.0%	6 18.8%	11 21.2%	0.730
Sclerodactyly	1 5.0%	2 6.2%	3 5.8%	1.000
Telangiectasia	2 10.5%	3 11.1%	5 10.9%	1.000
	Place of life		Total	<i>p</i>
	Bordeaux	Martinique		
N	38	34	72	
≥ 1 DM manifestation	18 54.5%	11 57.9%	29 55.8%	1.000
Gottron's sign	8 24.2%	8 42.1%	16 30.8%	0.220
Heliotrope rash	9 27.3%	6 31.6%	15 28.8%	0.760
Nail pain (manicure sign)	7 21.2%	4 21.1%	11 21.2%	1.000
Shawl sign	9 27.3%	2 10.5%	11 21.2%	0.290
Photo-sensibility	8 24.2%	3 15.8%	11 21.2%	0.726
Sclerodactyly	3 9.1%	0 0.0%	3 5.8%	0.291
Telangiectasia	5 16.1%	0 0.0%	5 10.9%	0.157

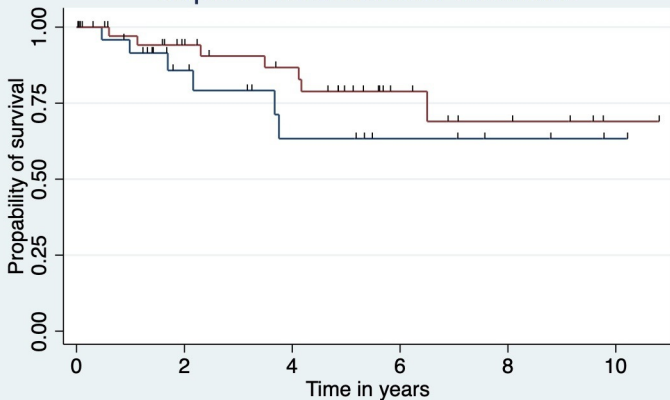
Supplemental Table 2. Comparison of Patients' Characteristics and Disease Evolution Between Patients From Bordeaux (Caucasians) and Martinique (Afro-Caribbean).

Variable (n)	Bordeaux 38		Martinique 34		p-value
Antibodies					0.031
Anti-PL7 +	20	52.6	9	26.5	
Anti-PL12 +	18	47.4	25	73.5	
Age (yr.) (mean SD)	63.5	12.9	54.3	13.4	0.006
Female sex (n %)	22	57.9	28	82.4	0.039
Connors' criteria					
ILD	31	83.8	30	90.9	0.485
Arthritis/arthralgia	30	78.9	32	94.1	0.090
Myositis	21	55.3	18	52.9	1.000
Raynaud's phenomenon	19	50.0	14	41.2	0.486
Mechanic's hands	15	39.5	14	41.2	1.000
Fever	11	28.9	10	29.4	1.000
Severe weakness (MRC \leq 3/5) (n, %)	14	36.8	5	14.7	0.059
CK level max (mean – SD)	1136.4	2337.2	2598.4	3603.5	0.007
Dyspnea at first visit (n %)	33	86.8	28	82.4	0.746
Severe dyspnea (NYHA \geq 3) at first visit (n %)	5	13.2	14	41.2	0.009
First PFT available (mean, SD)					
DLCO	52.2	18.4	46.4	25.4	0.617
FEV1	77.5	24.7	62.7	21.0	0.018
FVC	73.9	22.9	58.0	15.8	0.014
TLC	73.2	19.2	61.6	24.0	0.010
Fibrosis evolution (n %)	16	48.5	11	42.3	0.793
Severe dyspnea (NYHA \geq 3) at the end (n %)	9	24.3	7	23.3	1.000
Esophageal involvement	21	55.3	22	64.7	0.476
Pericardial effusion / myocarditis (n=67)	4	11.1	8	25.8	0.200
Pulmonary hypertension (n=66)	7	19.4	12	40.0	0.101
Neoplasia	4	10.5	5	14.7	0.727
Anti-SSA (Ro52)	19	50.0	22	64.7	0.240
ICU admission during follow-up (n %)	9	23.7	7	20.6	0.784
Death (n %)	7	18.4	7	20.6	1.000

Abbreviations: n, number; SD, standard deviation; yr, years; ILD, interstitial lung disease, MRC score, Medical Research Council 5-point scale score (0–5); NYHA, New York Heart Association; CK, creatine kinase; ICU, intensive care unit; DLCO, diffusing capacity of the lungs for carbon monoxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; PFT, pulmonary function test (by percentage of predicted value [%pred]); TLC, total lung capacity.



Kaplan–Meier survival estimates



Number at risk	
dot = Anti-PL7	28
dot = Anti-PL12	40

14	8	5	3	1
27	22	9	5	1



At least one of the following six criteria

ILD	Arthritis / arthralgia	Myositis	Raynaud's phenomenon	Mechanic's hands	Unexplained fever
Specific pattern on chest CT	Joint pain Synovitis (clinical, Xray or US of joints)	Muscle weakness Myositis on muscle biopsy Elevated CK Myogenic changes on EMG	Colour changes on fingers or toes +/- nailfold capillaroscopy	Hiker feet thickened and cracked skin on fingertips	≥37,8°C for >10 days, with no concomitant infection

Detectable anti-PL7 or anti-PL12 autoantibody

Consider PL7⁺/PL12⁺ Antisynthetase Syndrome

AT DIAGNOSIS

- **ILD severity:** pulmonary function tests and 6-minute walk
- **Heart involvement (pulmonary hypertension/pericarditis/myocarditis):** EKG + troponin/BNP levels + echocardiography +/- cardiac MRI
- **Malignancy screening:** abdominal and pelvis CT + digestive endoscopy + dermatology consultation + PSA (if high risk)/mammography/cervical cancer screening

MILD DISEASE

Stable ILD
Mechanic's hands
Raynaud's phenomenon
Unexplained fever

Close follow-up
Symptomatic treatment

MODERATE DISEASE

Chronic or stable ILD
Mild or moderate arthritis
Mild or moderate myositis

Oral +/- IVHD steroids
+ MMF or AZA or CNIs

RTX or IV-CYC
Or MMF (or AZA) + CNIs

Multi-disciplinary meeting :
abatacept or tofacitinib or Jak inhibitor

SEVERE DISEASE

Acute or subacute ILD
Severe arthritis or myositis

IVHD then oral steroids + CNIs

IVHD then oral steroids + CNIs
+ IV-CYC

Multi-disciplinary meeting :
RTX, tofacitinib,
plasma exchange, lung transplantation

LIFE-THREATENING DISEASE

Rapidly progressive ILD
Dysphagia or respiratory muscle involvement

FOLLOW-UP

- **ILD severity :** Chest CT (every 6 months then 1/yr), PFTs + 6MW (1/yr)
- **Heart involvement:** (1/yr)
- **Malignancy screening repeated in the year following diagnosis**

Discuss antifibrotic drugs in case of fibrosis