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Autoimmune interstitial lung disease in Latin-America

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ABSTRACT

Information about the prognosis and natural history of autoimmune interstitial lung diseases (Ai-ILD) is limited. The aim of the study was to evaluate the characteristics of patients diagnosed with Ai-ILD in Latin-America. We conducted an ambispective multicenter cohort study in 25 centers of Argentina, Colombia, and Uruguay between January 2015 and April 2018. Participants were included in the study if they had diagnosis of Ai-ILD performed by a multidisciplinary team. Patients were classified into the following sub-groups: connective tissue disease-associated ILD (ILD-CTD), interstitial pneumonia with autoimmune features (IPAF), and positive antineutrophils cytoplasmatic antibodies associated ILD (ILD-ANCA). All images were reviewed by a blinded thoracic radiologist. Out of the 381 patients included during the study period, 282 (74%; 95% CI; 69.39–78.16) were women. Mean age was 58 years old (SD 16). Three-hundred and twenty-five (85.1%; 95% CI 81.39–88.5) patients were classified as ILD-CTD (rheumatoid arthritis 31%, systemic sclerosis 29%, dermatomyositis 15%). Thirty-six patients were classified as IPAF (9.5%; 95% CI 6.9–12.8), and 13 (3.5%; 95% CI 2–5.75) as ILD-ANCA. Fifty percent of patients (95% CI 45.12–55.43) had a mild decrease of the forced vital capacity at the time of diagnosis. The most common treatment strategy was the combination of steroids and cyclophosphamide (30.1%; 95% CI 25.32–35.34) followed by azathioprine (20,3%; 95% CI 16.32–25.14). In conclusion, to the best of our knowledge, this is the first study to evaluate the characteristics and treatment strategies used in patients affected by Ai-ILD in Latin-America. Future studies should to evaluate the prognosis and impact of current treatment strategies in patients with Ai-ILD.

1. Introduction

Interstitial lung diseases (ILD) [1–6] with autoimmune phenomena (Ai-ILD) include ILDs associated with well-defined connective tissue diseases (ILD-CTD), interstitial pneumonia with autoimmune features (IPAF), and ILD associated with anti-neutrophil cytoplasmatic antibodies (ILD-ANCA) [7,8]. In all of them, lung injury is induced by an autoimmune mechanism that may be controlled with a timely immunosuppressive treatment [4,8–15].

The prevalence, clinical and radiological features along with the natural evolution of Ai-ILD as whole are not entirely known as most of the studies available are limited to specific subsets of patients such as those with ILD-CTD, IPAF or ILD-ANCA [16–27]. The aim of this study was to evaluate the clinical, radiological, functional, serological and therapeutic features of patients diagnosed with Ai-ILD in Latin America.

1.1. Materials and methods

1.1.1. Study design and characteristics of participating centers

We conducted an ambispective multicenter cohort study in 25 hospitals from Argentina, Colombia, and Uruguay between January 2015 and April 2018. The protocol was approved by the Institutional

Abbreviations: Ai-ILD, autoimmune interstitial lung diseases; CPFE, combined pulmonary fibrosis and emphysema.; DLCO, carbon monoxide diffusing capacity; DM/PM, dermatomyositis; FVC, forced vital capacity; HRCT, chest high-resolution computed tomography.; ILD-ANCA, positive anti-neutrophils cytoplasmatic antibodies associated ILD; ILD-CTD, connective tissue disease associated ILD; IPAF, interstitial pneumonia with autoimmune features; LIP, lymphocytic interstitial pneumonia; NSIP, non-specific interstitial pneumonia; OP, organizing pneumonia; PFT, pulmonary function test.; RA, rheumatoid arthritis; 6MWT, six minute walk test.; SSc, systemic sclerosis; UD, undifferentiated.; UIP, usual interstitial pneumonia

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Committee for the Review of Research Studies (CIREI) of the Hospital Privado de Comunidad and the Central Ethics Committee of the Province of Buenos Aires (File: 2919/1372/2016). All participants provided informed consent prior to the initiation of the study.

All the facilities selected to participate provided specialized care for patients with ILD by a multi-disciplinary team. The multi-disciplinary team should involve professionals from different specialties (internists, radiologists, rheumatologists, pulmonologists and/or pathologists).

1.1.2. Objective

The main objective of this study was to describe the demographic, clinical, imaging, functional and serological features, as well as the treatments received by patients diagnosed with Ai-ILD in Latin America.

1.1.3. Population

Participants who were older than 18 years of age and were diagnosed with Ai-ILD according after the evaluation of a multidisciplinary team were invited to participate. Ai-ILD was defined as the presence of lung images suggestive of ILD in a chest high-resolution computed tomography (HRCT) (irregular inter and/or intralobular septal thickening, traction bronchiectasis, cyst images, ground glass opacities, etc.) associated with: 1) the presence of CTD defined according to international classification guidelines [28–31], or 2) the presence of IPAF according to the ERS/ATS criteria 2015 [7], or 3) the presence of ANCA [27,32] by indirect immunofluorescence ELISA confirmed (with or without manifestations of systemic vasculitis). Asymptomatic patients were classified as having sub-clinical ILD.

All the CT scans were evaluated by a specialist in radiology focused in chest disease, who was blind to the participant medical history or suspected diagnosis. All patients had baseline lung function studies performed at baseline (6 min walk test (6MWT), spirometry and carbon monoxide diffusing capacity (DLCO)) and during follow-up.

Data on the different immunosuppressive treatment regimens, corticosteroid pulse therapy requirements and cumulative dose in the first 6 months, drugs used and the reason for treatment modification (toxicity, extra-pulmonary manifestation, ILD lack of response or progression) were recorded.

1.1.4. Variables and follow up

The following variables were collected:

- Demographic factors (sex, age, risk of occupational ILD)
- Clinical: Co-morbidities (diagnosis of heart failure according to the Framingham criteria [33] or echocardiogram, asthma according to the GINA [34] guidelines, chronic obstructive pulmonary disease (COPD) according to the GOLD [35] guidelines), pulmonary hypertension with a PASP > 50 mmHg according to doppler echocardiography, smoking, influenza and/or pneumococcal vaccination, previous exposure to pneumotoxic drugs, date of onset of symptoms, first treating professional of the multi-disciplinary team, date of Ai-ILD diagnosis.
- Serological data: the following data were recorded: antinuclear antibodies (ANAs) (titer and pattern) by IFI performed on Hep-2 cells, rheumatoid factor (RF) (nephelometric and turbidimetric methods), anti-DNA (IFI on crithidia luciliae or ELISA), Anti-cyclic citrullinated peptide (anti-CCP) by immunoassay, Anti-Ro/Ssa, Anti-La/Ssb, Anti-RNP, Anti-Sm, Anti-Scl-70 by ELISA or Westhern Blot, ELISA detected ANCA-MPO and ANCA-PR3. The request for anti-tRNA synthetase autoantibodies, anti-PM-Scl, and anti-MDA-5 antibodies was not mandatory.
- ILD tomographic pattern: only patients with high resolution computed tomography with a slice width of 2 mm maximum were included, and slices in mediastinal window were added. The tomographic patterns were classified as: usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP), organizing pneumonia (OP), combined NSIP/OP pattern, lymphocytic interstitial pneumonia (LIP), combined pulmonary fibrosis and emphysema (CPFE), and undifferentiated (UD).
- Pulmonary function test (PFT): Forced vital capacity (FVC) measured by spirometry before diagnosis (if any), at baseline (at the time of diagnosis), at the beginning and 3, 6, 12 months after the initiation of each treatment schedule (if any). The study was carried out by qualified technicians or pneumonologists and the best FVC value obtained was considered. FVC was expressed in absolute values, in liters, and as a percentage of the theoretical value. NHANES III equation (http://www.cdc.gov/niosh/topics/spirometry/nhanes.html) was used to calculate the predicted values.

DLCO was obtained with the single-breath technique; and desaturation in the 6MWT.

- Therapeutic schemes: ongoing immunosuppressive treatment regimens, corticosteroid pulse therapy, and cumulative dose in the first 6 months, drugs used and reason for treatment modification (toxicity, extra-pulmonary manifestation, ILD lack of response or progression).

1.2. Statistical analysis

Ratios and the corresponding 95% confidence intervals (95% CI) were estimated for the dichotomized variables, while mean and standard deviation (SD) were determined for the continuous variables. For comparisons, we run Chi-Square tests with Yates' correction, Fisher's Exact test mid P, and Student's *t*-test, as appropriate. All analyzes were conducted using StatsDirect (United Kingdom).

2. Results

During the study period, 381 participants were enrolled of which 48 (12.6%) had incomplete data. Female participants predominated (74%, 95% CI 69.39–78.16) with an average age of 58 years (SD 16). Forty four percent (95% CI 39.45–49.38) of the participants were current smokers or had previously smoked. The prevalence of pulmonary hypertension diagnosed by echocardiography was 10.75% (95% CI 8.03–14.27).

The most frequent diagnosis was ILD-CTD, accounting for 85.3% (95% CI 81.39–88.5) of all cases, followed by IPAF 9.5% (95% CI 6.9–12.8), and ILD-ANCA 3.5% (95% CI 2–5.75) (Table 1). Regarding ILD-CTD, the most frequent condition was rheumatoid arthritis (RA) 31% (95% CI 26.29–36.3), followed by systemic sclerosis (SSc) 28.6% (95% CI 23.97–33.76). As far as the respiratory function is concerned, the following values were obtained: an average baseline FVC of 2.35 L (SD 0.7) at diagnosis, 70% of the theoretical value (SD 18.3), and an average DLCO of 57.37% (SD 19.5). An 14% (95% CI 10.76–17.94) of the participants presented severe restriction at the time of diagnosis, while 50.28% (95% CI 45.12–55.43) had mild restriction.

The most frequent tomographic pattern was non-specific interstitial pneumonia (NSIP) accounting for 51.08% (95% CI 45.65–56.49) of all cases followed by usual interstitial pneumonia (UIP) with 21.36% 95% CI 17.24–26.15). Table 2 shows the most frequent patterns of the different autoimmune entities.

The most widely therapeutic scheme used was the administration of corticoids plus cyclophosphamide 30.1% (95% CI 25.32–35.34) followed by azathioprine (20,3%; 95% CI 16.32–25.14). Corticosteroid pulses were used in 39.8% (95% CI 34.59–45.27) of the participants as initial therapy. Rituximab was the first-line therapy option in 4.4% (95% CI 2.63–7.23) and, in 8.46% (95% CI 5.88–12) of the participants, it was the second-line therapy. After 6 months, 64.57% (95% CI 59.64–69.2) of the participants required no modification of the initial treatment scheme, while 16.54% (95% CI 13.14–20.6) had to modify their scheme due to worsening of symptoms or radiological progression.

Table 1
Clinical characteristics of the cohort.

	Ai-ILD (n = 381)
Women, n (%)	282 (74)
Age, mean (SD)	58 (16)
Smoking, n (%)	169 (44)
IPAF	36 (9.5)
ANCA-ILD	13 (3.5)
CTD-ILD	325 (85)
RA	101 (31)
SSc	93 (29)
DM/PM	50 (15)
Comorbidities, n (%)	
CHF	18 (5)
Asthma	13 (3)
COPD	17 (4)
Serological data, n (%)	
ANA	231 (60.6)
RF	145 (38)
Anti-CCP	91 (24)
Anti-Ro/Ssa	78 (20.5)
Tomographic pattern, n (%)	
NSIP	165 (51)
UIP	69 (21)
NSIP/OP	33 (10)
Functional parameters; mean (SD)	
Baseline %FVC	70 (18.3)
Baseline %DLCO	57.4 (20)
Treatments, n (%)	
Cyclophosphamide	96 (30)
Azathioprine	65 (20.4)
Mycophenolate Mofetil	55 (17)
Rituximab	14 (4.4)

CHF: congestive heart failure, COPD: chronic obstructive pulmonary disease, ANA: antinuclear antibodies, RF: rheumatoid factor, Anti-CCP: Anti-cyclic citrullinated peptide, AR: rheumatoid arthritis, SSc: systemic sclerosis, DM/PM: dermato/polymyositis, NSIP: non-specific interstitial pneumonia, UIP: usual interstitial pneumonia, NSIP/OP: non-specific interstitial pneumonia/organizing pneumonia overlap,% FVC: percentage of forced vital capacity,% DLCO: percentage of carbon monoxide diffusing capacity.

Table 2
Radiological pattern according to autoimmune entity.

Base disease and tomographic pattern	Percentage (%)
Rheumatoid arthritis (n = 101)	
UIP	40
NSIP	27
Others	17
Systemic sclerosis (n = 93)	
NSIP	73
UIP	13
Others	13
IPAF (n = 36)	
NSIP	64
UIP	12
Others	24

NSIP: non-specific interstitial pneumonia, UIP: usual interstitial pneumonia, IPAF: interstitial pneumonia with autoimmune features.

3. Discussion

EPIMAR is the Latin American cohort aimed to describe the characteristics and treatment used in those affected with Ai-ILD.

In our cohort, we observed a clear predominance of middle-aged women, in both ILD-CTD and IPAF patients. This result is in line with other ILD-CTD series but differs from some IPAF series, in which the male/female ratio was similar [17,36–40]. High smoking frequency (41%) similar to that of the general population and that described in the literature [17,38,39], was found.

The most frequent CTDs were RA and SSc, probably due to the high prevalence of RA in the general population and the high incidence of ILD in SSc context. In other descriptive studies of ILD-CTD, both diseases were also the most frequently detected [17,36].

The mild respiratory function involvement at baseline of most patients could indicated that the diagnosis had been made on a timely manner for treatment, thus preventing progression to more severe stages. The early detection of the disease was probably explained by the assistance and follow-up by a multidisciplinary team. Collins et al. evaluated 15 patients with IPAF and 20 patients with ILD-CTD and observed a baseline FVC of 68.7% and 71.4% respectively, which is in line with the results obtained in our study [17].

As regards the tomographic pattern, 51% of the patients presented a NSIP pattern, NSIP/OP and/or OP superimposition, which indicates a predominantly inflammatory involvement that can be treated and eventually reverted.

ILDs are complex and multifaceted pathologies that are currently best addressed by multidisciplinary teams in order to achieve a comprehensive diagnosis of the patients [41–44]. ILDs related to immunological mechanism that do not meet the classification criteria for a particular CTD have received different names in recent years [45–48]. Finally, a consensus classification criteria was developed and the term IPAF was coined [7], to help define and study this disease entity more uniformly. ILD-CTD, IPAF and ILD-ANCA share a common pathophysiological mechanism: *an autoreactive immune system* that, regardless of the nosological term used, applies a similar therapeutic strategy. IPAF and ILD-ANCA could even be early, incomplete or abortive forms of ILD-CTD and of ANCA-associated vasculitis [49]. Early identification and treatment of these clinical conditions could be the platform to interrupt their full expression and modify the evolution of the underlying autoimmune disease. This is the basis on which we grouped these 3 entities in our cohort under the term auto-immune ILD (Ai-ILD). To our knowledge, there are no multicenter studies in the literature reporting on patients in this way. This term had previously been proposed by Collins et al. [50].

Our study has limitations. It was conducted at specialized centers in these conditions so we cannot exclude selection bias. Even though patients were followed on a prospective basis, some of the data was retrieved retrospectively from the medical records. The diagnostic tests for the baseline immunological diseases and ILD were performed at each center and not using a standardized central laboratory. Images were reviewed in a centralized and blind fashion; however, they may not have had the same resolution. The population under study was only representative of the participating countries. Finally, the clinical and functional changes of patients over time could not be properly assessed due to the lack of standardized procedures for the follow-up of these patients.

4. Conclusions

EPIMAR is an important first step for the registration of patients with autoimmune-featured interstitial lung disease. To the best of our knowledge, this is the first Latin American multicenter cohort study comprising facilities with experience in ILD management. Further prospective studies should be conducted for a more comprehensive evaluation of the evolution of these diseases and the impact of the treatments used.

Conflicts of interest

Raffo covered the expenses of conducting the study.

Authorship

All authors contributed equally to the conduction of the study and

the writing of this manuscript.

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Appendix A. ANNEX 1

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