# "Usual" interstitial pneumonia with autoimmune features: a prospective study on a cohort of idiopathic pulmonary fibrosis patients

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## Abstract

### Objective

*The classification interstitial pneumonia with autoimmune features (IPAF) includes patients with interstitial lung disease (ILD) associated with autoimmune characteristics insufficient to reach classification criteria for a specific autoimmune disease (SAD). These criteria are divided into three domains: clinical, serological and morphological. The latter domain does not include the usual interstitial pneumonia (UIP) pattern, which is deemed not to be significantly associated with SAD. Therefore, the enrolment of these patients is more difficult, requiring at least one item from both of the other domains. The objective of this study is to evaluate the rate of progression towards SAD of a cohort of UIP patients satisfying only one IPAF domain (we called this group "UIPAF") compared with classic idiopathic pulmonary fibrosis (IPF).*

### Methods

*We prospectively enrolled IPF patients with radiologic and/or histologic UIP pattern, followed jointly by rheumatologists and pulmonologists from January 2017 to January 2021, with a minimum follow-up of 12 months.*

### Results

*We enrolled 190 IPF patients, 38 (20%) of whom were classified as UIPAF. IPF and UIPAF patients were similar for general characteristics, severity and prognosis, at presentation and at annual check-up. However, 28.9% of UIPAF patients progressed towards SAD, compared with 2% of IPF patients ($\chi^2=30.4$, $p\leq0.0001$).*

### Conclusion

*The association between a single clinical or serological domain of IPAF and UIP pattern is predictive for the development of a SAD if compared with isolated UIP. ILD can be the first manifestation of SAD, even with a UIP pattern, therefore, the morphological domain of IPAF criteria could be removed.*

**Key words**

interstitial pneumonia with autoimmune features, idiopathic pulmonary fibrosis, usual interstitial pneumonia, undifferentiated connective tissue disease, diagnosis

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## Introduction

Interstitial pneumonia with autoimmune features (IPAF) is a research classification arising from a joint consensus statement produced by the European Respiratory Society and the American Thoracic Society that aimed to create a consensus for the classification of patients with interstitial lung disease (ILD) associated with autoimmune characteristics not sufficient to achieve the classification criteria for a specific autoimmune disease (SAD) (1). This consensus is based on 3 domains: clinical, serological and morphological. This latter domain includes evidence of a histological and/or radiological pattern compatible with non-specific interstitial pneumonia, organising pneumonia and lymphocytic interstitial pneumonia. IPAF can be defined by the association of one of these ILD patterns with at least one item from the other two domains. Conversely, the usual interstitial pneumonia (UIP) pattern needs at least one item from both the clinical and serological domains. This distinction was made by the authors of the IPAF criteria, believing that they should not completely exclude UIP patients, but that this pattern does not significantly increase the likelihood of developing an SAD (1). Previous retrospective studies showed a significant number of UIP patients included in the IPAF classification (2). However, in prospective studies the proportion of UIP patients was significantly lower (3-5). The need to have at least two IPAF items, as well as the limited number of IPAF items in prospective cohorts, could explain the lower proportion of UIP-IPAF patients. Currently there are no available studies aimed at investigating the role of the morphological domain *per se* in the context of IPAF criteria.

The aim of this study is to evaluate the rate of progression towards SAD of a prospective cohort of patients with idiopathic pulmonary fibrosis (IPF) with a classical UIP pattern on high-resolution computed tomography (HRCT) associated with a single IPAF domain (clinical or serological). These patients, not classifiable as IPAF, were named UI-PAF, and compared with classic IPF patients (without IPAF items).

## Study design and methods

### *Populations*

We conducted a prospective cohort study approved by the local Ethics Committee; the patients gave their written consent to participate. We enrolled consecutive idiopathic UIP patients, diagnosed and managed as IPF, according to the latest versions of the current guidelines (6, 7). Diagnosis and follow-up were performed by a multidisciplinary team composed of a pulmonologist, a rheumatologist and a radiologist, all trained in the clinical activity of the "Regional Referral Centre for Rare Lung Diseases", Catania, Italy. The UIP patients were evaluated at least at the time of diagnosis and then after three and twelve months, and those who satisfied only one of the clinical or serological IPAF domains were named "UI-PAF". All patients included in the study were studied following a standardised flow-chart described below.

### *Clinical assessment*

In order to exclude possible specific causes that could explain ILD (*e.g.* environmental or pharmacological exposures) each patient was evaluated jointly by a pulmonologist, a rheumatologist and a radiologist. The presence of suggestive symptoms and signs of ILD (*e.g.* dry cough, dyspnea, wheezing, finger clubbing, basilar respiratory crackles) as well as a comprehensive medical history were collected. The patients were also studied for the presence of symptoms and/or signs suggestive of autoimmune conditions (*e.g.* sicca syndrome, arthritis, morning stiffness, skin manifestations, Raynaud's phenomenon), while HRCT scans were thoroughly reviewed by the radiologist.

Specific attention was paid by the rheumatologist to the presence of clinical signs of autoimmune conditions, and in particular those included in the clinical and serological domains of IPAF. To improve the specificity of the third clinical IPAF item, "Inflammatory arthritis or polyarticular morning joint stiffness ≥60 min" (1), it was only considered present in those patients with a clear inflammatory arthritis at the clinical assessment, or morning stiffness associated with an elevation of the erythrocyte sedimenta-

tion rate (ESR) and/or C-reactive protein (CRP) (8). Moreover, Raynaud's phenomenon (RP) was considered present in accordance with the 2014 international consensus criteria (9).

The evaluation of a possible development of SAD was performed by the rheumatologist at least every year or according to clinical need as evaluated by the pulmonologist.

*Pulmonary function tests*

All patients underwent pulmonary function tests (PFTs) including spirometry, diffusing lung capacity of carbon monoxide (DLCO) and the 6-minute walk test (6MWT) according to specific guidelines (10-12). Patients were considered to have severe ILD in the presence of DLCO ≤35% of the predicted and/or forced vital capacity (FVC) ≤50% (13). PFTs were performed with SentrySuite 2.15.147 (CareFusion Germany 234 GmbH Leibnizstrasse 7 D-97204 Hoechberg) and repeated at least every 4 months.

*Laboratory assessment*

At the time of the first assessment patients were invited to perform a laboratory assessment to exclude an underlying pre-existing autoimmune condition. The first line assessment according to our flowchart is the following: complete blood count, ESR, CRP, alanine aminotransferase, aspartate aminotransferase, creatinine phosphokinase, lactic dehydrogenase, myoglobin, urine test, creatinine, complement fractions C3 and C4, serum protein electrophoresis, rheumatoid factor, anti citrullinated protein antibody, antinuclear antibodies (ANA) in indirect immunofluorescence with description of pattern, anti-dsDNA, myeloperoxydase and PR3-anti neutrophil cytoplasm antibodies, and anti-extractable nuclear antigens. This latter panel included the following antibodies: Anti Jo1, anti-Ro/SSA (52k and 60k), anti-La/SSB, anti-Sm, anti-RNP, CENP and anti-Scl70.

A further immunological study included myositis specific and myositis associated antibodies. This panel included anti-synthetase antibodies, Pm/Scl and MDA5 but also other antibodies not included in IPAF criteria such as Mi2, Ku, SRP and Tiff1gamma. This part of the study was performed on selected patients where idiopathic inflammatory myopathies (IIMs) were suspected. It was performed in the presence of typical skin features, increased muscular enzymes, ANA positivity with nucleolar, cytoplasmic or mitochondrial pattern, positivity for Anti-Ro52k, and/or suggestive nailfold videocapillaroscopy (NVC) not associated with scleroderma antibodies (14).

These exams were performed at the first evaluation and repeated at least annually to understand the possible progression towards SAD.

*High-resolution computed tomography*

All patients underwent HRCT with slices ranging from 1.25mm to 2.5mm proving the presence of ILD with a UIP pattern at the first visit. HRCT was performed and evaluated by an expert radiologist and pulmonologist according to the current definition of the radiological patterns of ILD (15). HRCT was repeated during the follow-up, based on the clinical necessity evaluated by pulmonologists.

*Complementary exams*

Both pulmonologists and rheumatologists involved in the study were free to perform all those examinations deemed useful to exclude other conditions able to explain the presence of ILD. All patients with RP or skin rashes suspected for IIM or scleroderma spectrum disorders, or elevation of muscular enzymes were studied with NVC. The exam was performed with VideoCap 3.0 (DsMedica, Milan, Italy Viale Monza 133, 95125). NVC was defined positive in the presence of avascular areas (distance between two capillaries ≥500 μ) and/or giant capillaries (capillaries with a homogeneous diameter ≥50 μ). Neoangiogenesis was also recorded (capillaries with loops directed in three different directions) (16). Patients with xerophtalmia and/or xerostomia were studied for the presence of exocrine glandular impairment with appropriate tests (*e.g.* Schirmer's test or unstimulated whole saliva rate) considered useful for the diagnosis of primary Sjögren's syndrome (pSS) according to classification criteria (17). Other tests including electromyography, histological examinations (on lung, kidney and minor salivary glands) were performed when deemed useful to improve diagnostic accuracy.

*Diagnosis of autoimmune conditions*

The diagnosis of a SAD was an exclusion criterion at the first assessment. New autoimmune characteristics appearing three months after the first clinical evaluation were considered concomitant. The diagnosis of SAD was based on the specific validated classification criteria endorsed by the American College of Rheumatology/European League Against Rheumatism updated to the last versions. The sole condition currently without validated criteria is antisynthetase syndrome (AS). In this case we referred to the Solomon criteria (18).

All doubtful cases were further discussed in the Multi-Disciplinary Team, regularly held at least every two weeks. Considering the research nature of the current classification of IPAF, after the exclusion of secondary causes associated with ILD, UIP patients were all considered to be affected by IPF and treated following the current standard of care. Patients stopped anti-fibrotic treatment only in the case of subjective intolerance or refusal. The development of SAD after the diagnosis of IPF and the beginning of anti-fibrotic treatment did not result in an immediate discontinuation of treatment. These cases were discussed within the multidisciplinary team to better evaluate lung and systemic involvement, risks, benefits, disease activity and severity, and eventual side effects of treatment. In most of the cases patients maintained anti-fibrotic treatment, in some cases adding immunosuppressant drugs.

*Statistical analysis*

The data were presented in proportion or in median (1-3 Inter Quartile Range, IQR). We performed a Shapiro-Wilk test to evaluate the distribution of the data. Considering the non-normal distribution, non-parametric tests were used ($\chi^2$ test for binomial variables, Mann-Whitney U-test for continuous

variables). The statistical analysis was performed with IBM SPSS Statistics for Windows, v. 20.0 (Armonk, NY, USA: IBM Corp.).

## Results

The study included 190 patients who satisfied the inclusion criteria, of which 38 were UIPAF (20%). In the majority of cases, UIPAF patients showed only one autoimmune item included in the IPAF criteria (35, 92.1%), 2 patients showed 2 items (one with RP and mechanic's hands, another with ANA and Pm/Scl positivity), whereas only one patient showed 3 items (ANA, anti RNP, anti Sm). The proportion of IPAF items is reported in Table I. Among items not included in IPAF classification, NVC was positive at baseline in 5.3% (2 patients) of UIPAF patients and 0% of IPF. Conversely, sicca syndrome was seen in only 4 patients, all in the IPF group (2.6%). None of these patients proved to have impairment of glandular function.

The clinical presentation of the two cohorts was similar for general characteristics (age, gender, smoking habit) and functional parameters (FVC, DLCO, meters in 6-minute walk test, need for oxygen support, proportion of severe disease at both the first assessment and after 12 months). Medians are reported in Table II.

During the follow-up, 3 patients developed a SAD out of the 152 followed (2%) in the IPF group and 11 out of 38 (28.9%) in the UIPAF group ($\chi^2$=30.4, $p \leq 0.0001$).

In the IPF group, 2 patients progressed towards pSS and 1 to Polymyositis (PM). The progression towards SAD occurred after the first year in 2 patients (one with PM and one with pSS), and after the second year in the other. Both patients progressed towards pSS referred sicca syndrome, but functional tests at baseline resulted negative. Schirmer Test resulted positive during follow-up, and the diagnosis was made with minor salivary gland biopsy.

In the UIPAF group, we observed 6 patients with rheumatoid arthritis (RA) and a single case of systemic sclerosis (SSc), AS, PM, granulomatosis with polyangiitis (GPA), and systemic lupus erythematosus (SLE). The progression was noted within the first year in 1 patient (with PM), in 8 patients within the second year (4 RA and 1 with GPA, SSc, AS), and after the second year in 2 patients (both with RA) (Fig. 1).

None of the three UIPAF patients with multiple autoimmune items developed a SAD. The autoimmune features associated with UIP-ILD in patients who progressed are reported in Table III. Notably, the patient who progressed towards PM had NVC positivity at baseline, whereas the patient who developed SSc showed NVC positivity during follow-up.

**Table I.** Prevalence of IPAF criteria in UIPAF.

| Item | Prevalence |
|---|---|
| Raynaud's phenomenon | 23.7% |
| Polyarticular morning joint stiffness ≥60 min+ inflammatory arthritis | 5.3% + 5.3% = 10.6% |
| Puffy fingers | 2.6% |
| Mechanic's hands | 5.3% |
| Gottron's sign | 2.6 % |
| Antinuclear antibodies + anticentromeric antibodies | 21% + 2.6% = 23.6% |
| Rheumatoid factor | 23.7% |
| Pm/scl | 5.3% |
| DsDNA | 2.6% |
| Anticitrullinated protein antibodies | 7.9% |
| RNP | 2.6% |
| Sm | 2.6% |

IPAF items not included in the table were not present in the cohort.

**Table II.** Clinical presentation of patients.

| Item | UIPAF (=38) | IPF (=152) | *p* |
|---|---|---|---|
| Female | 18.4% | 19.7% | 1 |
| Age | 69 (65.3-73) | 71.5 (66-76) | 0.13 |
| Smoke | 24 (0-40) | 15 (0-40) | 0.53 |
| Onset of the first symptom | 12 (4-18) | 6 (2-12) | 0.07 |
| FVC T0 | 82 (70.3-100) | 78 (66-94) | 0.26 |
| FVC T1 | 86 (62-100) | 79 (67-93.3) | 0.75 |
| DLCO T0 | 53.5 (46-66) | 58 (48-71) | 0.05 |
| DLCO T1 | 53 (39.3-66) | 56 (44-69.5) | 0.18 |
| 6-MWT, meters T0 | 425 (350-478.8) | 420 (350-475) | 0.73 |
| 6-MWT, meters T1 | 387.5 (225-475) | 400 (275-475) | 0.53 |
| $O_2$ need T0 | 40.5% | 27.2% | 0.16 |
| $O_2$ need T1 | 55.2% | 47.3% | 0.47 |
| Severe ILD T0 | 7.9% | 7.2% | 1 |
| Severe ILD T1 | 13.2% | 15.8% | 0.8 |
| Dead after T1 | 31.6% | 28.3% | 0.34 |

6-MWT: 6-minute walking test; DLCO: diffusing lung capacity for carbon monoxide; FVC: forced vital capacity; ILD: interstitial lung disease; $O_2$: oxygen; T0: at enrolment; T1: at the first check-up (one year).

**Table III.** Baseline IPAF items associated with the progression toward SADs in UIPAF population.

| Item | Proportion | SAD developed |
|---|---|---|
| Anticentromeric antibody | 1 (100%) | SSc |
| Polyarticular morning joint stiffness ≥60min | 2 (100%) | RA, RA |
| Raynaud's phenomenon | 3 (33.4%) | RA, PM, SLE |
| Antinuclear antibodies | 1 (12.5%) | AS |
| Rheumatoid factor | 3 (33.3%) | RA, RA, GPA |
| Anticitrullinated protein antibodies | 1 (33.3%) | RA |

AS: antisynthetase syndrome; GPA: granulomatosis with polyangiitis; PM: polymyositis; RA: rheumatoid arthritis; SAD: specific autoimmune disease; SLE: systemic lupus erythematosus
The column "proportion" includes the absolute number of cases that progressed toward SAD in the UIPAF population (proportion of patients that progressed to those enrolled with the specific criteria).

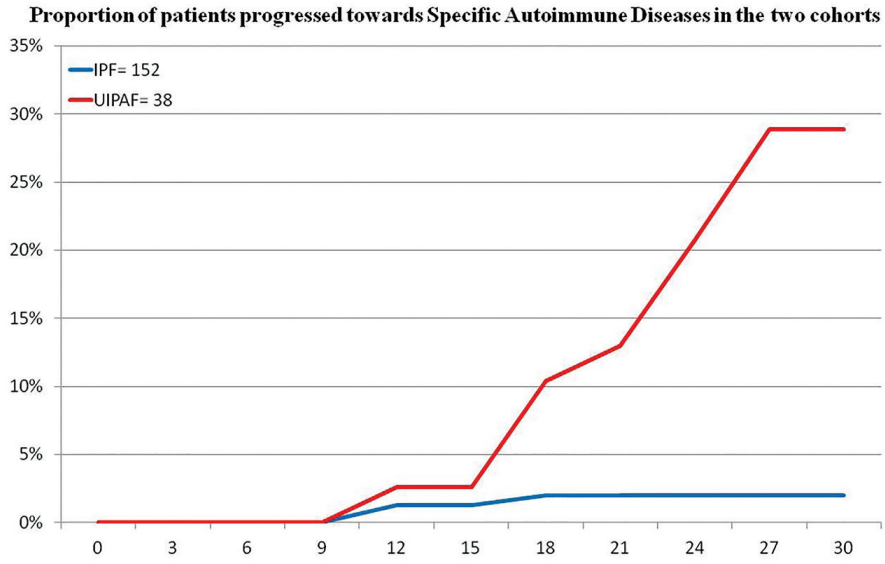


**Fig. 1.** Proportion of patients progressed towards specific autoimmune diseases in the two cohorts
IPF: idiopathic pulmonary fibrosis; UIPAF: usual interstitial pneumonia with autoimmune features.

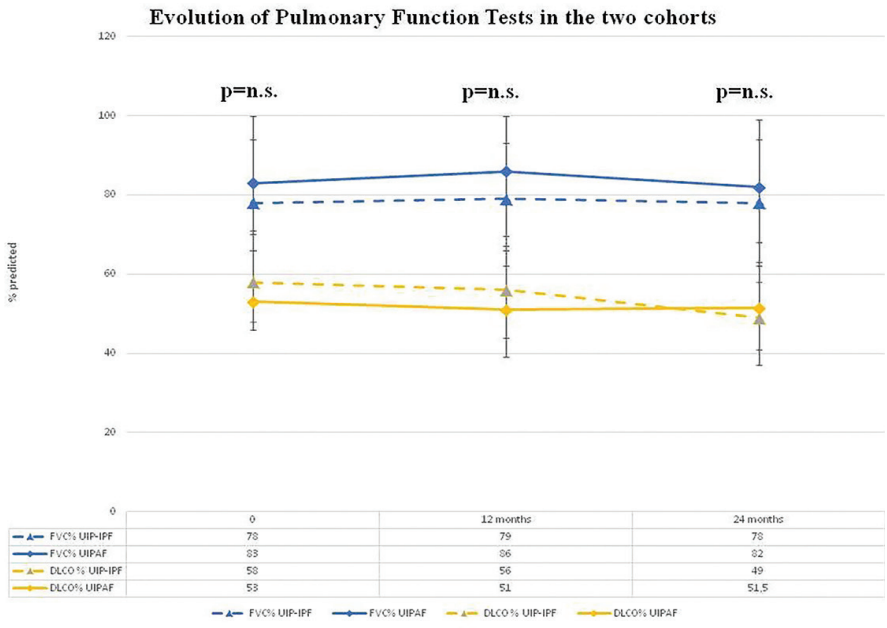


**Fig. 2.** Evolution of pulmonary function tests in the two cohorts.
DLCO: diffusion lung capacity for carbon monoxide; FVC: forced vital capacity; n.s.: not significant.

All the enrolled patients were treated with anti-fibrotic agents without significant differences in tolerance and clinical response.

During the follow-up, we did not note any difference as regards disease severity or mortality between UIPAF and IPF groups. A similar decline in FVC and DLCO was found in both groups (Fig. 2). A similar trend was also seen in patients that progressed towards SAD. Among them, four patients classified as UIPAF who developed RA (in 3 cases) and GPA died. The cumulative mortality at 3 years was 23.7% in the UIPAF group and 19.1% in IPF. Patients who progressed to SAD (14 subjects) showed a 3-year mortality of 21.4% (not significant).

## Discussion

In previous studies, we noted a low number of items in our IPAF prospective cohort: the majority of our IPAF patients had the morphological domain associated with only one other domain (clinical or serological) (3, 5). This study evaluated patients with a similar number of IPAF items, (satisfying only the clinical or serological domain), however with a UIP pattern. In line with this, we investigated whether the association of only one IPAF domain with a UIP pattern was sufficient to increase the rate of progression of these patients towards a SAD.

The UIPAF patients enrolled in this study seem to be indistinguishable from classic IPF as regards their clinical presentation and evolution: no differences were noted in general features, disease severity, response to antifibrotic treatment or mortality. The similarities seem to be maintained even after the development of SAD, suggesting that the major determinant of the prognosis in these patients is the UIP pattern of ILD. The presence of IPAF items, although insufficient to reach IPAF classification (this is the reason we used the term "UIPAF" to define our study population), selected a group of patients with a significantly higher probability of developing a SAD. A possible difference from "classical IPAF" can be noted in the kind of SAD developed. Actually, with the exception of the patients who progressed towards SSc and SLE, all the other patients developed a condition in which a UIP pattern is relatively common (PM and AS) or even prevalent (RA and GPA) (14, 19).

At the end of the study, 28.9% of UIPAF patients developed a SAD. This proportion is quite similar to that reported in previous studies on IPAF patients (2-5). Therefore, while a UIP pattern has clear prognostic significance, it is not sufficient for a diagnosis of IPF. Based on our results, the association of the clinical or serological domain is able to identify ILD patients going to a possible progression towards SADs, also with a UIP pattern.

In the IPAF criteria, the expert panel stated that a UIP pattern alone does not increase the likelihood of having connective tissue disease and therefore judged the presence of at least one feature from both the clinical and serological domains necessary to define an IPAF (1). However, in view of these new data, the presence of the morpho-

logical domain in the IPAF criteria could be questioned. Its removal could improve the accuracy of the criteria in enrolling ILD patients at risk for SAD and simplify the IPAF criteria (which are currently quite numerous).

Interestingly, in the IPF group, a small proportion of patients also developed SAD: 2 patients with pSS and one with PM. Several studies reported the possibility of ILD as a possible first manifestation of these diseases. In particular, ILD can precede the diagnosis of pSS by years. In these patients ILD is often in a UIP pattern, seronegative and associated with modest sicca syndrome (20-22). Currently, IPAF criteria do not include sicca syndrome or myalgia as possible items, however, a possible future revision of these criteria could include them, at least when they are associated with an instrumental demonstration (*e.g.* Schirmer's test or salivary gland ultrasounds for sicca syndrome, or increased serum muscular enzymes level in myalgia).

In conclusion, in our opinion the IPAF criteria have several merits. This research classification provides a homogeneous base to identify patients with an autoimmune flavour, in which to evaluate a possible lung onset of systemic SAD or incomplete forms of SAD. Despite the research scope of these criteria, their use in clinical practice has led to greater awareness about the possibility of a SAD. Therefore, improvements to IPAF criteria could have a further positive impact on clinical research for rheumatologists and pulmonologists; nonetheless, a tight collaboration between these two figures should be encouraged.

In view of possible improvements, an interesting recent article by Graham *et al.* (23) identified a different subset in IPAF patients positive for myositis specific antibodies, more similar to IIMs-ILD, suggesting the removal of these antibodies from the classification. Considering our results, the morphological domain could also be removed, adding (if anything) items able to improve accuracy in the enrolment of lung-onset of pSS and IIMs.

This is the first evaluation of the utility of the morphological domain in IPAF criteria. A possible strength of this study is the relatively large number of patients enrolled with a prospective design. Our unit could also have a clear perspective on IPAF patients, as it includes both pulmonologists and rheumatologists who are experts in autoimmune ILD working together. Possible limitations are the relatively low number of patients enrolled as UIPAF. New prospective, multicentre studies could recruit larger cohorts of these patients, evaluating also the possible influence of treatment on the development of SAD.

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