CHEST

Idiopathic Interstitial Pneumonia Associated With Autoantibodies

A Large Case Series Followed Over 1 Year

Bridget F. Collins, MD; Charles F. Spiekerman, PhD; Megan A. Shaw, MD; Lawrence A. Ho, MD; Jennifer Hayes, RN; Carolyn A. Spada, RN; Caroline M. Stamato, MPH; and Ganesh Raghu, MD

BACKGROUND: Some patients with autoimmune characteristics and idiopathic interstitial pneumonia, particularly usual interstitial pneumonia (UIP), do not fit neatly into the category of connective tissue disease-associated interstitial lung disease (CTD-ILD), idiopathic pulmonary fibrosis (IPF), or recently proposed yet to be validated criteria for interstitial pneumonia with autoimmune features (IPAF). Outcomes of these patients are unknown.

METHODS: This was a retrospective single-center study. Analyses of variance compared differences in mean change in FVC and diffusion capacity (D_{LCO}) over 1 year among 124 well-defined patients (20 patients with positive autoantibodies with or without symptoms of connective tissue disease [AI-ILD], 15 patients with IPAF, 36 patients with CTD-ILD, and 53 patients with IPF with negative CTD serologies [Lone-IPF]).

RESULTS: Of the patients, 75% with AI-ILD, 33% with IPAF, and 33% with CTD-ILD had UIP. Initial FVC and D_{LCO} were similarly moderately reduced across groups. Mean change in FVC over 12 months was as follows: −60 mL (IPAF), −110 mL (AI-ILD), −10 mL (CTD-ILD), and −90 mL (Lone-IPF) ($P = .52$). Mean change in D_{LCO} was as follows: 2.39 mL/mm Hg/min (IPAF), −1.15 mL/mm Hg/min (AI-ILD), −0.27 mL/mm Hg/min (CTD-ILD), and −1.05 mL/mm Hg/min (Lone-IPF) ($P < .001$). By pattern of disease, the mean change in FVC was as follows: −140 mL (UIP), 10 mL (nonspecific interstitial pneumonia), and 12 mL (unclassifiable/other) ($P = .001$).

CONCLUSIONS: No clinically significant differences in pulmonary function to distinguish between patients with AI-ILD, IPAF, CTD-ILD, and Lone-IPF were observed after 1 year. Longer periods of follow-up are needed to understand the outcomes of these patients. It is not yet clear whether AI-ILD is a distinct phenotype or a variant of the newly proposed entity IPAF.

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KEY WORDS: autoimmune interstitial lung disease; idiopathic pulmonary fibrosis; interstitial lung disease; interstitial pneumonia with autoimmune features

ABBREVIATIONS: AI-ILD = autoimmune interstitial lung disease; CILD = Center for Interstitial Lung Diseases; CTD = connective tissue disease; CTD-ILD = connective tissue disease-associated interstitial lung disease; D_{LCO} = diffusion capacity; ILD = interstitial lung disease; IP = interstitial pneumonia; IPAF = interstitial pneumonia with autoimmune features; IPF = idiopathic pulmonary fibrosis; Lone-IPF = IPF with negative CTD serologies; NSIP = nonspecific interstitial pneumonia; PFT = pulmonary function test; UIP = usual interstitial pneumonia; UWMC = University of Washington Medical Center

AFFILIATIONS: From the Center for Interstitial Lung Diseases (Drs Collins, Shaw, Ho, and Raghu and Mss Hayes, Spada, and Stamato) and the Institute of Translational Health Sciences (Dr Spiekerman), University of Washington Medical Center, Seattle, WA.

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CORRESPONDENCE TO: Ganesh Raghu, MD, University of Washington Medical Center, Center for Interstitial Lung Diseases, 1959 NE Pacific St, Campus Box 356175, Seattle, WA 98195; e-mail: graghu@uw.edu

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Although patients with connective tissue disease-associated interstitial lung disease (CTD-ILD) and idiopathic pulmonary fibrosis (IPF) have been relatively well characterized, less is known about patients who have interstitial pneumonia (IP) and positive serologies for connective tissue disease (CTD) but do not meet established diagnostic criteria for CTD.[1-4] This group has been described as undifferentiated CTD-ILD, autoimmune featured interstitial lung disease (ILD), lung dominant CTD, and most recently, interstitial pneumonia with autoimmune features (IPAF).[5-10] The 2011 evidence-based guidelines, while giving precise criteria for IPF, acknowledge that patients with usual interstitial pneumonia (UIP) and autoantibodies who do not meet criteria for a specific CTD are considered to have IPF in the appropriate clinical setting.[2] IPAF, based on serologic, clinical, and morphologic domains, was recently proposed in a research statement intending to create a more homogenous population of patients with IP and characteristics of autoimmune disease without CTD.[10] However, IPAF excludes a group of patients with positive autoantibodies with or without symptoms of CTD and IP (UIP in particular) not fulfilling IPAF criteria.

Although the UIP pattern is relatively common among patients with CTD-ILD, such as rheumatoid arthritis, and in studies of patients with IP with autoimmune characteristics, such as lung dominant CTD, presence of UIP alone is not included in the IPAF morphologic domain.[9,11] This does not mean that all patients with UIP are excluded from IPAF, but rather that UIP alone does not fulfill the IPAF morphologic domain. Therefore, a patient without one of seven symptoms in the IPAF clinical domain with positive autoantibodies and UIP would not currently be included in IPAF and presumably would be considered to have IPF. Acknowledging that the proposed IPAF criteria were consensus based, we think the proposed IPAF criteria should be broadened to include such a patient, or perhaps categorize such a patient as having autoimmune interstitial lung disease (AI-ILD).[12]

We sought to describe patients with AI-ILD and how these patients may or may not differ from those with IPAF in particular and from those with CTD-ILD and IPF with negative CTD serologies (Lone-IPF) by describing demographics, pattern of IP, and change in pulmonary function over time.

Methods

Study Design, Setting, and Subjects

This is a retrospective cohort study of adult patients seen at the Center for Interstitial Lung Diseases (CILD), at a tertiary referral center, at the University of Washington Medical Center (UWMC), from January 1, 2007 to March 31, 2013. All patients presenting to the CILD for new evaluation/management of ILD during the study period were screened. Four prespecified groups were identified (Table 1). Patients with IP and autoimmune characteristics were classified as (1) IPAF or (2) AI-ILD according to criteria in Table 1; groups 3 and 4 were CTD-ILD and IPF, respectively.[2,8,10] In addition to meeting 2011 guideline criteria, to meet criteria for IPF in our cohort, negative CTD serologies were required (Lone-IPF). The UWMC institutional review board approved this study (No. 44852).

Inclusion Criteria

Eligible patients were ≥ 18 years of age and had IP based on high-resolution CT images of the chest (inhalation/expiration images and supine/prone images). To avoid confounding and variability associated with testing technique and reference values between laboratories, we only included patients who had pulmonary function tests (PFTs) performed at the UWMC at initial CILD evaluation and 12 months later and who had serologic testing for CTD (all had antinuclear antibodies/patterns by immunofluorescence assay with reflexive panel, including anti-Sjogren syndrome related antigen A, anti-Sjogren syndrome related antigen B, antitopoisomerase 1, and antihistadyl-tRNA synthetase; rheumatoid factor; anticyclic citrullinated peptide antibody; and if available antineutrophil cytoplasmic antibody panel and myositis panel) at the UWMC Immunology Laboratory.

Exclusion Criteria

Patients with alternative explanations for ILD (eg, hypersensitivity pneumonitis, radiation treatment, drug-induced, occupation-associated, sarcoidosis), coexisting obstructive lung disease (FEV_1/FVC < 0.70), and emphysema greater than ILD on high-resolution CT chest images and comorbid lung conditions (eg, lung neoplasm, asthma, COPD) were excluded.

Outcomes

The outcomes of the study were the differences in mean change in absolute and percent predicted FVC and diffusion capacity (D_{LCO}) (corrected for hemoglobin) between 0 and 12 months.

Potential Confounding Factors

Potential confounding factors included age, sex, prior/current tobacco smoking, pulmonary hypertension by transesophageal echocardiogram or right heart catheterization, and abnormal acid gastroesophageal reflux by pH probe.

Statistical Analyses

Hypothesis tests were performed to compare outcomes between the groups (IPAF, AI-ILD, CTD-ILD, and Lone-IPF). Analysis of variance was used to compare change in means, and Pearson χ^2 test or Fisher exact test was used to compare proportions. For each patient, the difference in FVC or D_{LCO} between 0 and 12 months was calculated, and then the mean of these values was calculated and reported. If there was a statistically significant difference in overall group comparison, additional testing was performed to compare individual groups with each other. To protect against inflation of type I error, Tukey honest significant difference method (means), or

TABLE 1] Classification of Four Groups of Patients With Recognized Patterns of Interstitial Pneumonia

Disease Group	Diagnostic Criteria
Interstitial pneumonia with autoimmune characteristics	
IPAF	• Per IPAF criteria, interstitial pneumonia and exclusion of alternate etiologies and does not meet criteria of defined CTD, and one or more features from two or more of three domains ○ Clinical domain: seven extrathoracic features of CTD ○ Serologic domain: specific serum autoantibodies (including ANA ≥ 1:320 diffuse, speckled, or homogenous or any titer nucleolar or centromere pattern) ○ Morphologic domain: certain HRCT image patterns (NSIP, OP, NSIP with OP overlap, LIP) or histopathology pattern/features by surgical lung biopsy (NSIP, OP, NSIP with OP overlap, LIP, interstitial lymphoid aggregates with germinal centers, diffuse lymphoplasmacytic infiltration) or multicompartment involvement (unexplained pleural or pericardial effusion or thickening, intrinsic airway disease[a] or pulmonary vasculopathy)[b]
AI-ILD	• Interstitial pneumonia and exclusion of alternate etiologies and • Positive CTD serology at the UWMC Laboratory (including ANA ≥ 1:80) and • Did not meet IPAF criteria or criteria for specific CTD
CTD-ILD	• Interstitial pneumonia and • Met American College of Rheumatology or other defined/accepted criteria for CTD
IPF[d]	• Per 2011 evidence-based guidelines[c] ○ UIP or possible UIP on HRCT images ○ Exclusion of alternate etiologies: no history of exposures known to be associated with hypersensitivity pneumonitis, no signs/symptoms of CTD • Negative CTD serologies at the UWMC Immunology Laboratory

AI-ILD = autoimmune interstitial lung disease; ANA = antinuclear antibody; CTD = connective tissue disease; CTD-ILD = connective tissue disease-associated interstitial lung disease; HRCT = high-resolution CT; IPAF = interstitial pneumonia with autoimmune features; IPF = idiopathic pulmonary fibrosis; LIP = lymphoid interstitial pneumonia; Lone-IPF = IPF with negative CTD serologies; NSIP = nonspecific interstitial pneumonia; OP = organizing pneumonia; UIP = usual interstitial pneumonia; UWMC = University of Washington Medical Center.

[a]Intrinsic airway disease: airflow obstruction, bronchiolitis, or bronchiectasis.

[b]Of note, patients with UIP are not excluded from IPAF. The authors of the IPAF consensus criteria stated that "the presence of a UIP pattern alone does not increase the likelihood of having CTD"; therefore, presence of UIP did not meet the IPAF morphologic domain.[10]

[c]All patients diagnosed with IPF prior to 2011 met 2011 criteria.

[d]Designated as Lone-IPF because in addition to meeting 2011 IPF criteria, all patients with IPF had negative CTD serologies at the UWMC Laboratory.

the Bonferroni method (proportions), were used. Statistical significance was indicated for $P < .05$. Linear regression analyses adjusted for potential confounding covariates (age, sex, pulmonary hypertension, and outcome value at initial visit) were also performed. All statistical analyses were completed using SPSS 19.0 (IBM) and R version 3.1 (R Foundation for Statistical Computing).

Results

Cohort

Between January 2007 and March 2013, 124 patients (IPAF: n = 15, AI-ILD: n = 20, CTD-ILD: n = 36, and Lone-IPF: n = 52) referred to CILD met strict inclusion criteria. Table 2 shows the pattern of IP, serologic data, and symptoms for patients with AI-ILD. Most patients with AI-ILD had a UIP pattern of disease. These patients did not have detectable signs/symptoms of CTD that would fulfill the IPAF clinical domain other than joint pain, but this was attributed to degenerative joint disease because it was not clearly described as inflammatory in nature.

Demographic characteristics of all four groups are shown in Table 3. Overall, 53% of patients with IPAF, 40% with AI-ILD, 17% with CTD-ILD, and 62% with Lone-IPF were men ($P < .01$). Among patients in the CTD-ILD group, scleroderma spectrum disease and rheumatoid arthritis were the most common, accounting for 37.1% and 22.9%, respectively (data not shown). Patients with CTD-ILD were more often women than patients with IPAF and patients with Lone-IPF. On average, patients with Lone-IPF were older than those with IPAF and CTD-ILD, and those with AI-ILD were on average older than those with CTD-ILD (Table 3). More patients with Lone-IPF and AI-ILD were former/current smokers than those with

TABLE 2] Characteristics of 20 Patients With AI-ILD

Patient No.	Pattern of IP	Sex	Age, y	Autoantibodies	Symptoms
1	UIP	Male	61	ANA 1:160 speckled	Joint pains[a]
2	Other/unclassifiable	Female	52	ANA 1:80 homogenous	Joint pains (hands only)
3	UIP	Male	76	ANA 1:320 nucleolar	None
4	UIP	Male	66	RF, aldolase elevated	Recurrent sinusitis, hemoptysis caused by pulmonary capillaritis
5	UIP	Male	63	ANA 1:80 homogenous	None
6	UIP	Male	76	ANA 1:80 speckled	Joint pains
7	UIP	Female	62	ANA > 1:640 anticentromere	Hip pain, pruritic rash on face (below nose through chin)
8	UIP	Male	65	SSA	None
9	UIP	Female	72	ANA 1:640 nucleolar	Sicca symptoms, joint pains
10	UIP	Male	62	ANA 1:80 speckled, indeterminate SSA	None
11	UIP	Female	54	ANA 1:160 speckled	None
12	UIP	Female	73	ANA 1:80 homogenous	Esophageal dysmotility, joint pains
13	UIP	Female	60	ANA 1:160 homogenous, 1:40 speckled, Scl70 indeterminate	Generalized muscle weakness, fibromyalgia, joint pains
14	Other/unclassifiable	Female	57	CCP	None
15	NSIP	Female	59	RF	None
16	UIP	Female	51	ANA 1:320 speckled, 1:320 centromere, antichromatin, anti-RNP, anti-SmRNP	Sicca symptoms, dysphagia, joint pains
17	UIP	Male	76	ANA 1:80 nucleolar, indeterminate anti-RNP	Joint pains
18	NSIP	Female	76	CCP	Joint pains
19	UIP	Female	72	ANA 1:160 homogenous, RF	None
20	Other/unclassifiable	Female	27	ANA 1:1240 homogenous	None

ANA = antinuclear antibody; CCP = cyclic citrullinated peptide; IP = interstitial pneumonia; RF = rheumatoid factor; RNP = ribonucleoprotein; SmRNP = anti-Smith ribonucleoprotein; SSA = anti-Sjogren syndrome related antibody. See Table 1 legend for expansion of other abbreviations.
[a]Joint pains were not specifically described as inflammatory in nature and were therefore assumed to be more consistent with osteoarthritis/degenerative changes.

IPAF and CTD-ILD, but these differences were not statistically significant. The proportion of patients with pulmonary hypertension and gastroesophageal reflux disease did not differ significantly between the four groups. Initial FVC and D_{LCO} percent predicted were similar, and on average FVC was mildly reduced and D_{LCO} was moderately reduced.

Pattern of ILD

All patients had high-resolution CT chest images. ILD pattern was assessed by histopathology (surgical lung biopsy) in 80% of patients with IPAF, 35% with AI-ILD, 41.7% with CTD-ILD, and 75.5% with Lone-IPF. UIP was observed in all patients with Lone-IPF and most patients with AI-ILD (75%). Nonspecific interstitial pneumonia (NSIP) or an unclassifiable/other pattern was observed in most patients with IPAF and CTD-ILD (Table 4). The pattern of IP did not differ significantly between patients with CTD-ILD and IPAF, but did differ between patients with AI-ILD (75% with UIP) and CTD-ILD (33% with UIP; $P = .04$).

TABLE 3] Demographics and Baseline Pulmonary Function

Demographic	IPAF (n = 15)	AI-ILD (n = 20)	CTD-ILD (n = 36)	Lone-IPF (n = 52)	*P* Value[a]
Male	8 (53)	8 (40)	6 (17)	32 (62)	< .01[b]
Age, y	54.6 ± 11.8	62.2 ± 11.7	53.2 ± 13.8	63.2 ± 7.9	< .01[c]
Prior/current smoker	7 (47)	11 (55)	14 (39)	33 (63)	.14
Pulmonary HTN[d]	3 (20)	7 (35)	15 (42)	16 (31)	.48
GER[e]	12 (80)	15 (75)	26 (72)	41 (79)	.89
Initial FVC, mL	2,768 ± 1,208	2,623 ± 810	2,487 ± 910	2,926 ± 881	.17
Initial FVC, % predicted	68.7 ± 20.3	73.4 ± 19.7	71.4 ± 21.2	72.5 ± 16.6	.89
Initial DLCO, mL/mm Hg/min[f]	13.6 ± 5.1	12.4 ± 3.4	12.3 ± 4.6	13.7 ± 4.2	.34
Initial DLCO, % predicted[f]	45.7 ± 15.2	45.9 ± 13.1	45.1 ± 13.5	45.8 ± 12	.96

Values are mean ± SD, No. (%), or as otherwise indicated. GER = gastroesophageal reflux; HTN = hypertension. See Table 1 legend for expansion of other abbreviations.

[a]Overall *P* value for test of association between group and characteristic. Pearson χ^2 test was used for proportions. Analysis of variance was used for means. Post hoc testing was done to compare individual groups if the overall association was statistically significant. For proportions, a Bonferroni correction was applied. For means, the Tukey honest significant difference method was used.

[b]On post hoc test, CTD-ILD differed significantly from IPAF and from Lone-IPF.

[c]On post hoc test, IPAF differed significantly from IPF, CTD-ILD differed from Lone-IPF, and AI-ILD differed from CTD-ILD.

[d]Pulmonary HTN by transthoracic echocardiogram (estimated systolic pulmonary artery pressure > 35 mm Hg or mean pulmonary artery pressure > 25 mm Hg, with capillary normal wedge pressure by right heart catheterization).

[e]Abnormal acid GER by 24-hour pH probe (DeMeester score > 14.7).

[f]Corrected to hemoglobin.

Difference in Pulmonary Physiology at 0 and 12 Months

Mean change in FVC over 12 months ranged from −113 mL (AI-ILD) to −11 mL (CTD-ILD) (*P* = .70) (Tables 5, 6). Changes in FVC percent predicted over 12 months did not differ significantly between groups on unadjusted (analysis of variance) or adjusted analyses (linear regression) (Tables 5, 6). Mean change in DLCO and DLCO percent predicted over 12 months significantly differed between IPAF and each of the other groups on both unadjusted and adjusted analyses. There were not significant differences in mean change in DLCO or DLCO percent predicted between AI-ILD, CTD-ILD, and Lone-IPF on post hoc testing (Tables 5, 6).

We assessed for differences in mean change in FVC over 12 months between patients with UIP, NSIP, and other/unclassifiable patterns of IP (regardless of whether patients had IPAF, AI-ILD, CTD-ILD, or Lone-IPF) and found a mean change in FVC over 12 months

TABLE 4] Patterns of Interstitial Pneumonia/ILD[a]

Pattern of Interstitial Pneumonia	IPAF (n = 15)	AI-ILD (n = 20)	CTD-ILD (n = 36)	Lone-IPF (n = 52)	IPAF/AI-ILD, *P* Value[b]	IPAF/CTD-ILD, *P* Value	AI-ILD/CTD-ILD, *P* Value
	ILD Pattern, %						
UIP[c]	33	75	33	100	.14	.99	.04
NSIP[d]	27	10	34				
Fibrotic	20	5	17				
Cellular	7	5	17				
Other/unclassifiable	40	15	33				

Fisher exact test was used for association between groups (excluding IPF) and ILD pattern (UIP, NSIP, and other/unclassifiable) (*P* = .037). See Table 1 legend for expansion of abbreviations.

[a]All patients had HRCT images determined by histopathology obtained by surgical lung biopsy in 80% of patients with IPAF, 35% of patients with AI-ILD, 41.7% of patients with CTD-ILD, and 75.5% of patients with Lone-IPF.

[b]Pairwise comparisons (with Bonferroni correction).

[c]The definition of UIP pattern from Raghu et al.[2]

[d]The definition of NSIP pattern from Travis et al.[8]

TABLE 5] Analyses of Variance to Assess for Differences in the Mean Change in FVC and DLCO Between 0 and 12 months Among Patients With IPAF, AI-ILD, CTD-ILD, and Lone-IPF

Disease Group	FVC, mL			FVC, % Predicted		
	Mean	95% CI	*P* Value	Mean	95% CI	*P* Value
AI-ILD	−113	−264.0 to 38.0	.70[a]	−2.8	−6.2 to 0.6	.25[a]
IPAF	−58	−232.0 to 116.0		−0.7	−4.6 to 3.3	
CTD-ILD	−11	−123.0 to 102.0		0.2	−2.3 to 2.7	
Lone-IPF	−81	−175.0 to 14.0		−3.0	−5.1 to −0.8	
	DLCO Corrected to Hb, mL/mm Hg/min			DLCO Corrected to Hb, % Predicted		
	Mean	95% CI	*P* Value	Mean	95% CI	*P* Value
AI-ILD	−1.1	−2.0 to −0.3	< .001[b]	−3.9	−7.0 to −0.7	< .001[b]
IPAF	2.4	1.4 to 3.4		6.3	2.6 to 10.0	
CTD-ILD	−0.3	−0.9 to 0.4		−0.7	−3.1 to 1.7	
Lone-IPF	−0.9	−1.5 to −0.3		−2.9	−5.1 to −0.7	

DLCO = diffusion capacity; Hb = hemoglobin. See Table 1 legend for expansion of other abbreviations.
[a]Post hoc tests (Tukey honest significant difference) failed to indicate any pairwise group comparisons as significant.
[b]Post hoc tests (Tukey honest significant difference) showed IPAF significantly different from all other groups in DLCO ($P < .001$) and DLCO percent predicted ($P = .01$).

of −135 mL among patients with the UIP pattern, which was significantly greater than the mean change in FVC in patients with NSIP or other/unclassifiable pattern (Table 7). Patients with UIP also had a greater decrease in mean change in DLCO over 12 months than those with other/unclassifiable pattern.

Finally, we performed a subanalysis to assess for differences in mean change in FVC and DLCO among only those patients with UIP in each of the four groups (IPAF with UIP: n = 5, AI-ILD with UIP: n = 15, CTD-ILD with UIP: n = 12, and IPF with UIP: n = 52). Overall results were unchanged from those previously mentioned (data not shown). We also compared patients within each group (AI-ILD, IPAF, and CTD-ILD) with UIP with those with non-UIP and did not find significant differences in mean change in FVC and DLCO over 12 months (Table 8).

TABLE 6] Linear Regression to Assess for Differences in the Mean Change in FVC and DLCO Between 0 and 12 Months Among Patients With IPAF, AI-ILD, CTD-ILD, and Lone-IPF

Disease Group	Difference[a] in Mean Change in FVC, mL			Difference[a] in Mean Change in FVC, % Predicted		
	Coefficient	95% CI	*P* Value	Coefficient	95% CI	*P* Value
AI-ILD	0[b]	…	.69	0[b]	…	.28
IPAF	48	−188.0 to 285.0		1.9	−3.5 to 7.3	
CTD-ILD	114	−83.0 to 311.0		3.3	−1.2 to 7.8	
Lone-IPF	37	−143.0 to 218.0		−0.3	−4.4 to 3.9	
	Difference[a] in Mean Change in DLCO Corrected to Hb, mL/mm Hg/min			Difference[a] in Mean Change in DLCO Corrected to Hb, %		
	Coefficient	95% CI	*P* Value	Coefficient	95% CI	*P* Value
AI-ILD	0[b]	…	< .001	0[b]	…	< .001
IPAF	3.6	2.2 to 5.0		10.2	5.2 to 15.2	
CTD-ILD	1.0	−0.2 to 2.1		3.1	−1.1 to 7.3	
Lone-IPF	0.2	−0.9 to 1.3		0.9	−3 to 4.9	

See Table 1 and 5 legends for expansion of abbreviations.
[a]Adjusted for patient age, sex, presence of pulmonary hypertension, and outcome value at initial visit.
[b]Comparison category.

TABLE 7] Analyses of Variance to Assess for Differences in the Mean Change in FVC and DLCO Between 0 and 12 Months Based on Pattern of IP (Regardless of Diagnosis)

Pattern of IP	FVC, mL			FVC, % Predicted		
	Mean	95% CI	*P* Value	Mean	95% CI	*P* Value
UIP	−135	−208 to −63	.003[a]	−3.6	−5.2 to −2.0	.001[a]
NSIP	10	−141 to 161		0.8	−2.7 to 4.2	
Other/unclassifiable	116	−13 to 244		2.4	−0.5 to 5.4	
	DLCO Corrected to Hb, mL/mm Hg/min			DLCO Corrected to Hb, % Predicted		
	Mean	95% CI	*P* Value	Mean	95% CI	*P* Value
UIP	−0.74	−1.26 to −0.22	.04[b]	−2.3	−4.1 to −0.4	.16[c]
NSIP	0.22	−0.80 to 1.25		0.67	−2.9 to 4.3	
Other/unclassifiable	0.48	−0.41 to 1.37		0.67	−2.5 to 3.8	

See Table 1, 2, and 5 legends for expansion of abbreviations.
[a]Post hoc tests (Tukey honest significant difference) showed UIP was significantly different from other/unclassifiable ($P = .002$) and marginally different from NSIP ($P = .053$).
[b]Post hoc tests (Tukey honest significant difference) showed UIP was significantly different from other/unclassifiable ($P = .30$).
[c]Post hoc tests (Tukey honest significant difference) showed no significant differences between any pair of groups.

Discussion

The IPAF criteria were introduced to characterize patients with IP and autoimmune characteristics for research purposes, and efforts to validate these criteria are ongoing prior to recommendation for use in routine clinical practice.[13-15] The proposed consensus-based criteria exclude some patients, particularly those with UIP (which does not fulfill the IPAF morphologic domain), with ILD and positive serologies who may have characteristics of CTD but do not meet one of

TABLE 8] Student *t* Tests to Assess for Difference in Mean Change in FVC and DLCO Over 12 Months Between Patients With UIP and Non-UIP Patterns in Each of Three Groups: AI-ILD, IPAF, and CTD-ILD

Change in Pulmonary Function	Non-UIP		UIP			Difference (UIP − Non-UIP)			*P* Value
	No.	Mean	95% CI	No.	Mean	95% CI	Mean	95% CI	
12-mo change in FVC, mL									
AI-ILD	5	−4	−209 to 201	15	−149	−346 to 47	−145	−201 to 491	.38
IPAF	10	−5	−150 to 140	5	−164	−504 to 178	−159	−53 to 371	.13
CTD-ILD	24	33	−80 to 127	12	−98	−318 to 121	−132	−6 to 270	.06
12-mo change in FVC, %									
AI-ILD	5	−1.4	−6.6 to 3.8	15	−3.3	−7.6 to 1.1	−1.9	−7.0 to 10.7	.65
IPAF	10	0.7	−3.0 to 4.4	5	−3.4	−10.9 to 4.1	−4.1	−1.4 to 9.6	.13
CTD-ILD	24	1.7	−0.7 to 4.1	12	−2.8	−7.7 to 2.0	−2.0	−0.1 to 9.2	.06
12-mo change in DLCO, mL/mm Hg/min									
AI-ILD	5	0.0	−1.8 to 1.8	15	−1.5	−2.5 to −0.5	−1.5	0.0 to 3.1	.06
IPAF	10	3.1	1.8 to 4.3	5	1.1	−0.7 to 2.8	−2.0	0.4 to 3.6	.02
CTD-ILD	24	−0.4	−1.3 to 0.4	12	0.0	−1.1 to 1.2	0.5	−1.8 to 0.8	.45
12-mo change in DLCO, %									
AI-ILD	5	0.8	−6.1 to 7.7	15	−5.4	−9.0 to −1.8	−6.2	−0.3 to 12.7	.06
IPAF	10	7.5	2.6 to 12.4	5	3.8	−2.4 to 10.0	−3.7	−3.3 to 10.7	.27
CTD-ILD	24	−1.3	−4.5 to 1.9	12	0.4	−3.6 to 4.4	1.7	−6.8 to 3.5	.51

See Table 1 and 5 legends for expansion of abbreviations.

seven clinical criteria in the IPAF clinical domain.[10] It is unknown if the patients we characterized as AI-ILD (IP and positive CTD serologies with or without symptoms suggestive of CTD not meeting IPAF criteria) will blossom into a specific CTD later in their course, if AI-ILD is a distinct phenotype, or if these positive autoantibodies are clinically insignificant. To our knowledge, this study is the first large case series to describe and compare mean change in FVC and D_{LCO} over 1 year in a well-defined cohorts of patients with IPAF, CTD-ILD, and Lone-IPF with AI-ILD.

We did not find significant differences in demographics to distinguish one group from another, other than patients with IPAF and CTD-ILD tended to be younger than those with AI-ILD and Lone-IPF. We also did not observe a clinically significant difference in mean change in pulmonary function over 1 year when comparing patients with IPAF, AI-ILD, CTD-ILD, and Lone-IPF. We observed an incremental increase in D_{LCO} over 12 months among patients with IPAF, whereas D_{LCO} decreased among patients with AI-ILD, CTD-ILD, and Lone-IPF on both adjusted and unadjusted analyses. Although this finding could suggest a trend supporting distinction of patients with IPAF from those in the other three groups, in particular AI-ILD, the differences we observed are arguably small to be clinically significant, given inherent variability in D_{LCO} measurements and lack of significant differences in FVC measurements.[2,16,17]

Among patients with IP and an autoimmune flavor to their disease in our cohort, 43% met criteria for IPAF, and the remaining 57% were classified as AI-ILD. Some patients with AI-ILD did have symptoms with an autoimmune flavor (eg, esophageal dysmotility; muscle aches, pain, and some weakness) that were not included in the proposed clinical domain of IPAF. We consider these patients as AI-ILD, distinguishing them from patients with true IIP or IPF. Others did not have symptoms suggestive of CTD and merely had positive autoantibodies, which would meet criteria for IPF diagnosis based on the current guidelines.[2] Classification of patients with autoantibodies and UIP without clinical manifestations of CTD is debated because circulating autoantibodies are present among healthy adult patients, particularly elderly individuals.[18,19] Studies of how these patients may or may not differ from the general IPF or IIP populations have had variable results, but suggest that patients with UIP and autoantibodies alone may differ from those with IPF.[20-22] Also, ILD may be the initial presenting symptom in some CTD.[1] A recent study of patients with CTD-ILD in China found that 14% of 288 patients with CTD-ILD initially presented with pulmonary symptoms.[15]

Some studies of patients with IP and autoimmune characteristics have found that patients with non-UIP ILD often had improvement in FVC over 1 year compared with worsening or no change among patients with UIP or IPF.[9,23,24] Approximately one-half of 71 of the patients with non-IPF in our cohort had UIP. If pattern of ILD plays a larger role in clinical course than specific diagnosis, this could account for why we did not observe statistically significant differences in mean change in FVC over 12 months between the four groups. We did, in fact, observe that all patients with UIP in our cohort had a significantly greater mean decline in FVC over 12 months than all of those with non-UIP patterns. To assess whether UIP might have similar implications for clinical behavior among patients with AI-ILD, IPAF, and CTD, we compared mean change in pulmonary function over time between subgroups of only patients with UIP (IPAF with UIP, AI-ILD with UIP, CTD-ILD with UIP, and IPF with UIP) and did not find significant differences. This could suggest that UIP has similar implications for clinical behavior among patients with IPAF, AI-ILD, and CTD-ILD. However, when we compared patients with UIP and non-UIP patterns within each of these three groups, there were not significant differences, and it is possible that these analyses were limited by small numbers in each subgroup.

Clinical disease behavior may depend on how IP with autoimmune characteristics is defined.[6,25,26] Similar survival behavior in studies of patients with IP with autoimmune characteristics and those with IPF in contrast to patients with CTD-ILD is likely associated with more frequent manifestation of UIP.[9,27,28] A recent abstract by Ahmad et al[29] did not find a significant difference in 1- and 2-year survival among patients with IPAF and IPF regardless of pattern of disease. In a validation cohort for IPAF, Oldham et al[13] did not observe an association between UIP and increased mortality among patients with IPAF in multivariable analyses, and survival among patients with IPAF did not differ significantly from that of patients with IPF. Based on these findings and our results, factors beyond pattern of ILD or changes in pulmonary function may be driving previously observed similarities and differences in clinical behavior among these patients. Additional analyses, likely involving biomarkers and genetic studies, are needed. Although future studies might provide

insight into clinical behavior of these cohorts, it seems premature to exclude UIP from the morphologic domain of IPAF.

Our study was not designed to assess any specific treatment regimen and was undertaken before availability of pirfenidone and nintedanib for treatment of IPF (patients were not participating in clinical trials for either medication). Some patients with Lone-IPF and AI-ILD were receiving triple therapy with prednisone/azathioprine/N-acetylcysteine in the context of clinical standard of care at the time or the PANTHER-IPF (Prednisone, Azathioprine, and N-Acetylcysteine: A Study That Evaluates Response in Idiopathic Pulmonary Fibrosis) trial; however, triple therapy was subsequently not associated with change in rate of FVC decline over time when compared with placebo.[30]

Limitations include the retrospective and observational nature of this single-center study, albeit a center with recognized expertise in evaluation and management of ILD. There is selection bias because we deliberately included only patients with all PFTs and serologic testing performed at our center. Although this greatly reduced the sample size to a relatively small proportion of the large number of patients seen at CILD during the study period, we took this approach to ensure consistency of PFT technique, reference values, and adherence to American Thoracic Society standards over time and allow accurate comparison within patients and between groups. Finally, the study design and sample size of the cohorts do not allow meaningful conclusions to be drawn regarding treatment effects or mortality; however, multiple clinical trials of ILD in the setting of scleroderma and IPF have used an end point of change in FVC over 1 year.[31-35] An additional limitation is that only a proportion of patients with AI-ILD were formally evaluated by a rheumatologist at the UWMC for confirmation/evaluation of their rheumatologic symptoms, if present. Specific information from the patients who may have been evaluated by an outside rheumatologist was not available to us. Finally, although patients entered the cohort at the time of initial presentation to the CILD, patients were not at a uniform point in their disease course or duration of symptoms; some were newly diagnosed, and others had been previously diagnosed and were presenting for further evaluation and management recommendations.

Conclusions

Our results suggest that patients with AI-ILD more closely resemble those with IPF than those with IPAF. Given the small numbers and small differences in change in pulmonary function over time that are likely not clinically significant, we did not find evidence to support exclusion of patients with AI-ILD from studies of those with IIP and an autoimmune flavor to their disease. Our results suggest that further study over longer periods of time is necessary prior to exclusion of patients with AI-ILD from future studies of patients with IPAF. It is important to study patients with phenotypes that are less clear because patients with idiopathic NSIP or cryptogenic organizing pneumonia are often already treated with immunomodulatory therapies. In the interim, we believe patients with AI-ILD should be included in ongoing and future studies aiming to understand clinical course and outcomes of patients with IP and an autoimmune flavor to their disease rather than placed in the category of IPF or IP by default.

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