J R Coll Physicians Edinb 2020; 50: 247–55 | doi: 10.4997/JRCPE.2020.307 REVIEW

Interstitial pneumonia with autoimmune features

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Abstract

Interstitial lung disease (ILD) is an umbrella term for lung disease characterised by inflammation and fibrosis of the interstitium. ILD can be idiopathic or secondary to connective tissue disorders, drugs or environmental exposures. Before labelling it as idiopathic we have to rule out secondary causes. ILD is one of the most common extra-articular manifestations of connective tissue diseases (CTDs), causing significant morbidity and mortality. Patients with pre-existing CTD can develop ILD; some patients develop ILD against the background of either one or two clinical features of a CTD or isolated auto-antibody positivity. The current terminology for such an entity is interstitial pneumonia with autoimmune features (IPAF). The current criterion is based on three domains: clinical, serologic and morphologic. To satisfy the IPAF classification criteria, one needs to satisfy the mandatory criterion with one feature from two of the three domains.

Classifying patients with this criterion helps in early initiation of immunosuppression and in monitoring them closely for development of features of a well defined CTD. There are a few limitations like the clinical domain being more skewed towards systemic sclerosis and inflammatory myositis, exclusion of antineutrophilic cytoplasmic antibody (ANCA) and cytoplasmic pattern in antinuclear antibody (ANA). There are no clear protocols for treatment of IPAF and most of the data has been extrapolated from the management of systemic sclerosis (SSc) ILD and idiopathic non-specific interstitial pneumonia (NSIP). Progressive disease in spite of treatment demands stronger immunosuppressive agents. Studies on the role of antifibrotics in IPAF are underway, with few small studies showing positive outcomes. There are conflicting reports on the survival and outcome of the IPAF cohort. Certain studies suggest that they have better survival compared with idiopathic pulmonary fibrosis (IPF) though other studies contradict this statement.

Keywords: connective tissue disorder, interstitial lung disease, interstitial pneumonia with autoimmune features, idiopathic pulmonary fibrosis, CTD–ILD, HRCT chest

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Introduction

Interstitial lung disease (ILD) comprises a group of disorders characterised by inflammation and fibrosis of the lung interstitium. 'Diffuse parenchymal lung disease' (DPLD) is considered to be a more appropriate term, as ILD is more of a radiographic term and most of these diseases are not restricted to the lung interstitium.[1] We shall use the term ILD in this review considering the familiarity of the term with the readers. In this review, we discuss the classification criteria of IPAF, its limitations, the change in management and outcome based on the prompt identification of this subset and also the need for close follow-up.

Classification of diffuse parenchymal lung diseases:[1,2]

1. DPLD of known cause (e.g. connective tissue disease [CTD]-associated ILD, due to drugs etc.)
2. Idiopathic interstitial pneumonia (IIP)
   a. Idiopathic pulmonary fibrosis (IPF)
   b. IIP other than IPF (idiopathic non-specific interstitial pneumonia, desquamative interstitial pneumonia, cryptogenic organising pneumonia, acute interstitial pneumonia, rare and unclassifiable idiopathic interstitial pneumonias)
3. Granulomatous DPLD (e.g. sarcoidosis)

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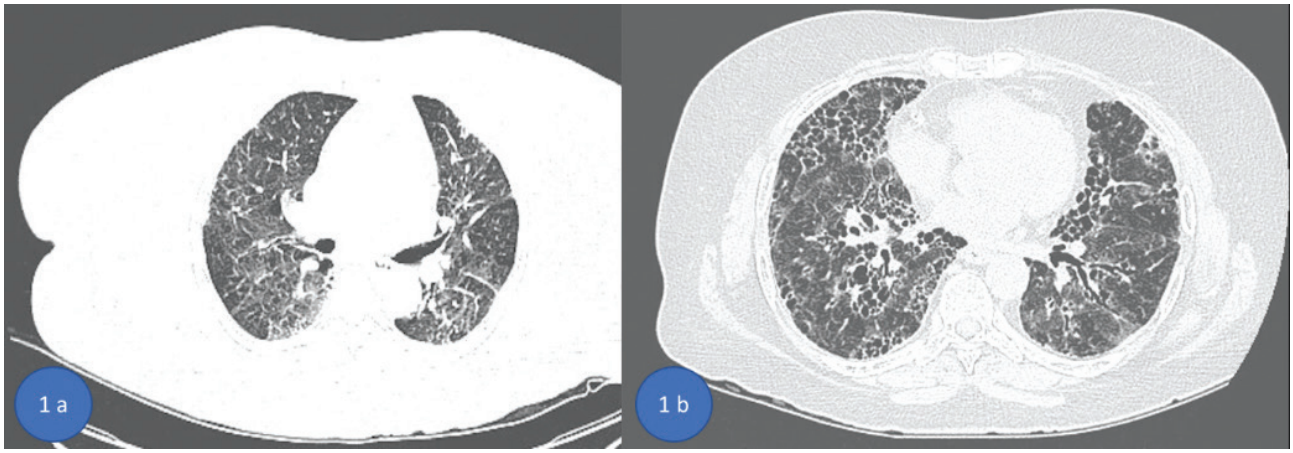
Figure 1a Depicting the NSIP pattern with ground glass opacities
Figure 1b Depicting the UIP pattern with honey combing and traction bronchiectasis



4. Others (e.g. lymphangioleiomyomatosis)

Before labeling the patients as having idiopathic pulmonary fibrosis (IPF), we have to look for various identifiable causes including autoimmune variants. ILD is one of the major extra-articular manifestations of CTDs, causing significant morbidity and mortality. CTD-ILD is one of the common causes of an underlying ILD accounting for 30% cases. The frequency varies with the disease, with prevalence more common in systemic sclerosis compared with other CTDs.[3]

The prognosis, outcome and treatment varies between these groups (CTD-ILD vs IPF), hence the need for prompt identification. We also have autoimmune variants in between which do not satisfy the criteria for CTD-ILD or IPF. Though various terms were used initially, the current classification criteria label them as interstitial pneumonia with autoimmune features (IPAF).

Search strategy

We searched the Medline database for English-only texts with the following keywords: interstitial pneumonia with autoimmune features (IPAF), interstitial lung disease (ILD), connective tissue disorder associated ILD (CTD-ILD), lung-dominant CTD, non-specific interstitial pneumonia, SSc-ILD, idiopathic pulmonary fibrosis (IPF), immunosuppressives /anti-fibrotics in ILD, undifferentiated connective tissue disorder (UCTD). We included the relevant publications (original articles, clinical trials/randomised controlled trials, review articles) from the last five years with regards to treatment, outcome and prognosis. We also included prior landmark publications concerned with classification criteria and major drug trials.

Case scenario 1

A 45-year-old female presented with breathlessness on exertion. On evaluation, the patient had anti-Scl-70 positivity, and a non-specific interstitial pneumonia (NSIP) pattern (Figure 1a) of ILD on high resolution computed tomography (HRCT) chest. This patient would have a score of 5 according to the 2013 classification criteria for systemic sclerosis so cannot be classified as having SSc (requires a total score of 9).[4] So, how do we classify this patient? Can we name it as evolving/early SSc (CTD-ILD) or as lung-dominant CTD or as UCTD? Does it matter? Does the treatment change with the classification or the term used? What happens if the same patient had an usual interstitial pneumonia (UIP) pattern (Figure 1b) on HRCT chest?

CTD-ILD vs UCTD vs IPAF

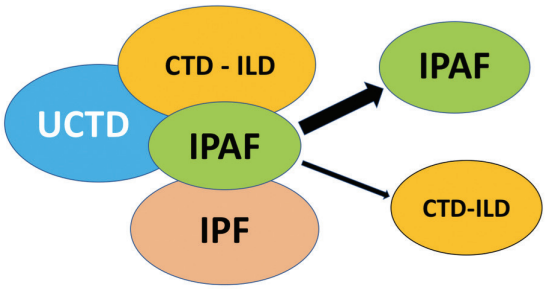
A patient with a new-onset ILD with features of a CTD satisfying the ACR classification criteria of the concerned CTD is classified as CTD-ILD. We may also have patients not satisfying the classification criteria for a CTD. What is UCTD, and how should it be defined? Preliminary criteria to define UCTD are 1) signs and symptoms suggestive of a connective tissue disease, but not fulfilling the criteria for any defined CTDs, 2) positive antinuclear antibodies, and 3) disease duration of at least 1 year.[5] An average of 25% may evolve into a well-defined CTD usually in the first five years of follow-up. The common clinical features of UCTD are arthralgia, arthritis, Raynaud's phenomenon, leukopenia, thrombocytopenia and sicca symptoms. But 10% of these patients with UCTD overlap with ILD. If we compare the proposed diagnostic criteria for UCTD and current IPAF criteria, there is a significant overlap of clinical and serological features. IPAF and UCTD seem to be variants of the same disease spectrum except for the low incidence of ILD in UCTD.[6,7] The 'lung dominant CTD' (currently termed as IPAF) can be considered as a small subset of UCTD.[7] Some of them might evolve into a fully developed CTD with ILD or may remain as IPAF.[7] The overlap of IPAF with other disease cohorts and its evolution is depicted in Figure 2.

What we should know and why

We come across ILD in two subsets of patients:

1. On a pre-existing well-defined CTD such as: RA-ILD or systemic sclerosis-ILD
2. Referred from a pulmonologist to rule out a CTD in a newly diagnosed ILD patient

Figure 2 Pictorial representation depicting overlap of IPAF with CTD–ILD, UCTD and IPF. A small percentage of IPAF progresses to well-defined CTD–ILD but rest remain as IPAF.



UCTD: Undifferentiated connective tissue disease; IPAF: Interstitial pneumonia with autoimmune features; IPF: Idiopathic pulmonary fibrosis; CTD – ILD: Connective tissue disorder associated interstitial lung disease

The second subset could have three different courses. They might have an established CTD satisfying both clinical and serological criteria diagnosed by a rheumatologist for the first time. While others of the referred subset would not have any clinical features or any positive serological tests suggestive of a CTD, hence they would be diagnosed as IIP. The third possibility would be that they could have one or two clinical features suggestive of CTD or isolated antibody positivity (rheumatoid factor, ANA and others). A few of them could have one or two clinical features suggestive of CTD or isolated antibody positivity (rheumatoid factor, ANA and others).

So how do we classify such patients? There is a grey area between a well-established CTD-ILD and IIP/IPF. These diseases were given various names over the years and the latest classification refers to this group as IPAF.[8]

Classification criteria

In 2007 Kinder et al. used the term 'undifferentiated connective tissue disease (UCTD)' and proposed diagnostic criteria.[9] Fischer et al. later proposed the term 'lung dominant CTD (LD-CTD)' and the provisional criteria to diagnose occult CTD or CTD in evolution.[10] This criterion had no clinical features but included histopathological features with autoantibodies. In 2011 Vij et al. proposed a new term 'autoimmune-featured ILD (AIF-ILD)' and criteria for patients with ILD with one or more clinical and serological features.[11] Later in 2012 Corte et al. proposed UCTD diagnostic criteria to evaluate the relationship between UCTD and IIP (NSIP pattern on surgical biopsy).[12]

In 2015 the European Respiratory Society/American Thoracic Society (ERS/ATS) Task Force finalised the term 'interstitial pneumonia with autoimmune features (IPAF)' to describe the group of patients in the grey area of a possible CTD with ILD.[8] The task force had a multidisciplinary panel comprising a pulmonologist, rheumatologist, thoracic radiologist and a pulmonary pathologist. The term CTD was intentionally avoided to prevent giving a false impression that these patients have well defined CTD. The criteria is based on three domains and the complete criteria are discussed below.[8] In the current classification criteria of IPAF, one needs to satisfy the mandatory criteria plus one feature from two of the three domains.[8]

2015 European Respiratory Society/ American Thoracic Society classification criteria for IPAF[8]

The following three are mandatory criteria:

1. Presence of an interstitial pneumonia (by HRCT or surgical lung biopsy) and
2. Exclusion of alternative aetiologies and
3. Does not meet criteria of a defined connective tissue disease

In addition, at least one feature from at least two of these domains should be present; A. Clinical domain B. Serologic domain and C. Morphologic domain.

A. Clinical domain

1. Distal digital fissuring (i.e. 'mechanic hands')
2. Distal digital tip ulceration
3. Inflammatory arthritis or polyarticular morning joint stiffness ⩾60 min
4. Palmar telangiectasia
5. Raynaud's phenomenon
6. Unexplained digital oedema
7. Unexplained fixed rash on the digital extensor surfaces (Gottron's sign)

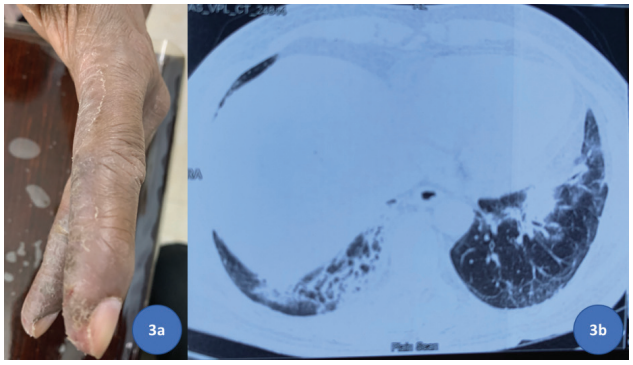
B. Serologic domain

1. ANA ⩾1:320 titre, diffuse, speckled, homogeneous patterns or a) ANA nucleolar pattern (any titre) or b) ANA centromere pattern (any titre)
2. Rheumatoid factor ⩾2× upper limit of normal
3. Anti-CCP
4. Anti-ds DNA
5. Anti-Ro (SS-A)
6. Anti-La (SS-B)
7. Anti-ribonucleoprotein
8. Anti-Smith
9. Anti-topoisomerase (Scl-70)
10. Anti-t RNA synthetase (e.g. Jo-1, PL-7, PL-12; others are: EJ, OJ, KS, Zo, t RS)
11. Anti-PM-Scl
12. Anti-MDA-5

C. Morphologic domain

1. Suggestive radiology patterns by HRCT (see text for descriptions):
   a. NSIP b. OP c. NSIP with OP overlap d. LIP
2. Histopathology patterns or features by surgical lung biopsy:
   a. NSIP b. OP c. NSIP with OP overlap d. LIP e. Interstitial lymphoid aggregates with germinal centres f. Diffuse lymphoplasmacytic infiltration (with or without lymphoid follicles)
3. Multi-compartment involvement (in addition to interstitial pneumonia):

Figure 3a and 3b 58-year-old male presented with mechanic hands (3a), ILD (UIP) (3b) and anti-Jo-1 antibody positivity – suggestive of an incomplete Anti-Jo-1 syndrome.



a. Unexplained pleural effusion or thickening b. Unexplained pericardial effusion or thickening c. Unexplained intrinsic airways disease (by pulmonary function tests, imaging or pathology) d. Unexplained pulmonary vasculopathy

In the clinical domain, most of the features are related to systemic sclerosis and anti-synthetase syndrome. In comparison to the previous criteria, some of the non-specific features like alopecia, photosensitivity have been excluded. The role of the physician/rheumatologist is more prominent with this domain, in identifying subtle clinical clues.[8]

The serologic domain included titre for both antinuclear antibody (ANA by IFA) and rheumatoid factor (RF), to increase the specificity. But for specific ANA patterns like centromere and nucleolar, it is considered significant irrespective of the titre. For all patients, an ANA profile has to be done including the extended myositis profile.

The morphologic domain has three sections. The first is the imaging section, where a pattern of NSIP, organising pneumonia (OP), lymphoid interstitial pneumonia (LIP) on HRCT chest should raise the suspicion of IPAF. UIP was not included as an IPAF-specific morphologic feature as it is not the common pattern in CTDs except in rheumatoid arthritis. Though a patient with a UIP pattern is not excluded, it is mandatory to have at least one feature from the clinical, serological or other section of the morphologic domain. The next section is the histopathologic evidence of interstitial pneumonia on surgical lung-biopsy specimens and again a UIP pattern was not included as an IPAF-specific feature. The last section is concurrent involvement of other thoracic structures like the pleura or pericardium in addition to interstitial pneumonia.[8]

Case scenario 1: If we apply the IPAF classification criteria to the 45-year-old female with ILD (NSIP pattern) and anti-Scl 70 antibody positivity, she will satisfy the criteria: mandatory criterion (ILD/ not satisfying the 2013 ACR–EULAR classification criteria for SSc4 /no alternative diagnoses) plus one each in two domains: serologic domain (anti-Scl 70 antibody positive) and morphologic domain (NSIP pattern on HRCT chest). But if the ILD is an UIP pattern, then the patient would not satisfy the IPAF criteria. Though a NSIP pattern is common in CT-ILD, we do see patients with an UIP pattern particularly more commonly in rheumatoid arthritis. Hence, in patients with an UIP pattern we need two more features from two different domains. Can we diagnose this patient as UCTD-ILD? Yes we can, but the incidence of ILD is lower in UCTD.

And we have the new term IPAF, which can be considered as the fraction of UCTD who present with ILD.

Advantages of the current IPAF classification criteria

To talk about its advantages, it makes both physician/rheumatologist and pulmonologist work up meticulously for an underlying connective tissue disorder when they diagnose an ILD. A uniform terminology like IPAF, which includes certain HRCT findings like organising pneumonia, NSIP, LIP, UIP, makes radiologists and other treating specialties aware of such an entity. This would lead to increased awareness, early diagnosis and better treatment protocols in years to come. Bringing ILD with few autoimmune features under IPAF might result in treatment with adequate immunosuppressants which might prevent progression of ILD. These cases would have been deprived of treatment before, particularly patients with NSIP and NSIP-OP for want of proper recommendations and labelling of disease.

Case scenario 2

A 58-year-old male presented with breathlessness on exertion and on evaluation had a UIP pattern of ILD in HRCT chest (Figure 3a). He did not have any other clinical symptoms. On clinical examination, the patient had mechanic hands (Figure 3b) and on serological testing tested strongly positive for anti-Jo1 antibody. Should we term this patient as having IPAF? He has a mandatory criterion (ILD with no alternative diagnoses and not satisfying the EULAR ACR classification criteria for myositis)[13] with one feature in the clinical domain (mechanic hands) and one in the serologic domain (anti-Jo1 antibody positivity).

Limitations of the current IPAF classification criteria

The disadvantages of the current classification of IPAF include:

Late recognition of serious auto-immune diseases like idiopathic inflammatory myositis and labelling them as IPAF (e.g. anti-Jo 1 per se is a myositis-specific antigen and the presence of which, along with ILD, needs a definitive protocol for treatment and a stronger immunosuppression).[14]

Case scenario 2: Though he satisfies the current IPAF criteria, he has anti-Jo-1 syndrome in evolution and needs an aggressive treatment with higher immunosuppressives.

The classification criteria does not include cytoplasmic pattern while defining an ANA by immunofluorescence

Table 1 Role of immunosuppressives and antifibrotics in the management of CTD–ILD and IPF

CTD–ILD Immunosuppressives are 'Indicated' Antifibrotics have been promising	**Idiopathic pulmonary fibrosis (IPF)** Immunosuppressives are 'Contraindicated' Antifibrotics are definitely indicated
Cyclophosphamide (Scleroderma Lung Study 1):[18] Oral cyclophosphamide (CYC) in comparison with placebo had significant improvement in FVC and symptoms. The benefit was sustained for 24 months even after stopping CYC at 12 months.	1. **PANTHER Study:**[25] Patients with idiopathic pulmonary fibrosis who were treated with prednisolone, azathioprine and N–acetylcysteine were found to have increased risk of death and hospitalisation. The study was aborted even before completion due to the increased incidence of deaths. 2. **ASCEND/CAPACITY**[26] study: Pirfenidone treatment vs placebo for 52 weeks reduced disease progression in IPF. 3. **INPULSIS**[26] study: nintedanib reduced the rate of FVC decline and hence slowed the diseases progression in IPF.
Mycophenolate mofetil (MMF)(Scleroderma Lung Study 2):[19] MMF (for 24 months) was equally efficacious as oral cyclophosphamide (for 12 months). Both groups had significant improvement in FVC. But, MMF was better tolerated with less toxicity.	
Azathioprine (FAST study):[20] Initially received 20 mg of prednisolone on alternate days and intravenous cyclophosphamide (600 mg/m^2) followed by maintenance with azathioprine. Though there was no significant improvement in primary and secondary points, there was a positive trend in FVC towards improvement.	
Rituximab (EUSTAR network study):[21] Rituximab was studied in patients with systemic sclerosis over a period of 2 years, there was no major improvement in FVC values in comparison to controls. But on secondary analysis, they felt rituximab in combination with MMF may be more effective for SSc-ILD. Rituximab was also found to be beneficial in CTD–ILD, particularly in specific subsets like anti-synthetase syndrome.[22]	
Antifibrotics: Pirfenidone (LOTUSS trial):[23] Safety and tolerability of pirfenidone in combination with MMF was demonstrated	

CTD-ILD: connective tissue disorder associated interstitial lung disease; IPF: idiopathic pulmonary fibrosis; FVC: forced vital capacity; CYC: cyclophosphamide; MMF: mycophenolate mofetil; SSc: systemic sclerosis

under serological domain. Since cytoplasmic pattern can be associated with definitive ILD (anti-synthetase syndrome-anti-Jo-1 antibodies), in a resource deprived country where positivity by ANA by IF alone demands a complete ANA profile workup, non-inclusion of cytoplasmic pattern in ANA may lead to a missed diagnosis of IPAF.[15]

Presence of anti-MDA-5 antibodies in serology, the availability of which is not uniform in most countries may lead to difficulties in classification.

Though the mandatory criterion includes all ILD patterns (UIP inclusive), the radiological pattern under morphology does not include UIP. We are well aware that UIP is associated in many of our CTDs like systemic sclerosis (similar to case scenario 1) and rheumatoid arthritis and few cases may even benefit from immunosuppression. The authors of the classification system have answered this query saying 'since there is no morphological credit associated with UIP, it needs additional clinical and serological positivity to qualify into IPAF.[16]

The clinical domain is skewed towards systemic sclerosis and inflammatory myositis with no mention of sicca symptoms, which might also be noted in some ILD patients and needs following up.

Other than this, we do have a set of patients with antineutrophilic cytoplasmic antibody (ANCA), (commonly anti-myeloperoxidase [MPO]) positivity and ILD who do not come under any category and may benefit from immunosuppressive treatment.[17]

The authors acknowledged limitations of this IPAF criteria.[8] Firstly, the need for the above criteria to be tested on a larger cohort and validation. If needed, the criteria have to be revised or modified. They also felt that some of the diseases classified under IPAF might be considered as incomplete CTDs or disease in evolution.[8]

Does the treatment strategy differ?

In general, patients with CTD-ILD are considered to have a better prognosis in comparison to idiopathic pulmonary fibrosis. Most of these patients have NSIP as the common pattern with the exception of rheumatoid arthritis (UIP pattern). Controlled trials have been done in systemic sclerosis patients and the same data has been extrapolated in the management of other CTDs. We have discussed the relevant studies in patients with CTD-ILD and IPF in Table 1.

In between these two groups (CTD-ILD vs IPF) we have the IPAF patients. So, should we treat them with immunosuppressives? Is there any role for antifibrotics? Is

Table 2 Evidence available for treatment of IPAF and idiopathic NSIP has been discussed

Drugs	Salient points from available evidence
Steroids	0.5 mg/kg body weight (bw) to 1 mg/kg bw of prednisolone, to be tapered down to 5–10 mg/day by the end of 6 to 9 months. Prolonged low dose steroids in patients with rapid relapses. Fulminant disease requires pulse methylprednisolone (750 1000 mg/day for 3 days).[29] In the study by Park et al. initial dose of prednisolone was : Initial dose of prednisolone (51.5 ±12 mg/day); steroid dose reduced to 15 mg by 5.7 3.7 months; average duration of initial therapy (17.4 ±12.1 months).[30] Lee et al. enrolled 35 biopsy-proven NSIP patients and all were on steroids. Median dose was 0.54 mg/kg/day. 86% were steroid responders, of which, 80% improved and 20% were stable. Among steroid responders, 40% had a relapse or steroid dependency.[31]
Mycophenolate mofetil	In a study by Swigris et al. there was a significant improvement trend in FVC at 52, 104 and 156 weeks in 19 patients with lung dominant CTD. Median MMF dose: 3 g/day.[32] In a study by McCoy et al. MMF was useful in patients (n = 28 vs 24; MMF vs controls) with significant disease and progressive decline of lung function. MMF was found to attenuate disease progression in IPAF, particularly in patients with more of GGO and less of reticulation on HRCT. Median MMF dose: 2 g/day.[33]
Azathioprine	Azathioprine is usually started at a dose of 25 mg and increased slowly to a maximum of 150 to 200 mg/day. No major studies are available for the usage of azathioprine in IPAF.[26,29]
Cyclophosphamide	Kondoh et al. studied effect of oral cyclophosphamide (1–2 mg/kg/day) with low dose prednisolone (20 mg/day on alternate days) in patients with fibrotic NSIP (n = 27) vs IPF (n = 12). Patients with fibrotic NSIP had a more favourable response and better survival than IPF.[34] Corte et al. studied the efficacy of intravenous cyclophosphamide (600 mg/m^2) in suspected or known cases of rapidly progressing NSIP. It was well tolerated and patients either improved or had a stable course.[35]
Antifibrotics	Huang et al. concluded that pirfenidone might be a good add-on treatment in IPAF if refractory to steroids and other immunosuppressives.[36] There are ongoing trials with pirfenidone (801 mg pirfenidone vs placebo three times daily for 24 weeks)[37] and nintedanib (INBUILD [nintedanib vs placebo]) in progressive fibrosing ILD.[38]
Others	In refractory disease with deterioration of lung function, after the first line immunosuppressives rituximab may be tried. Similarly, calcineurin inhibitors had good response in patients with associated inflammatory myositis. Other molecules like tocilizumab, abatacept have been tried in ILD associated with systemic sclerosis and inflammatory myositis.[39,40] There is an ongoing trial in patients with CTD–ILD (RECITAL [CYC vs RTX]).[41] Other options which may be considered in severe progressive disease are haematopoietic stem cell transplantation (variable results in each trial) and lung transplantation based on the experience in systemic sclerosis.[41]

ILD: interstitial lung disease; NSIP: non-specific interstitial pneumonia; IPAF: interstitial pneumonia with autoimmune features; CTD-ILD: connective tissue disorder associated interstitial lung disease; IPF: idiopathic pulmonary fibrosis; FVC: forced vital capacity; CYC: cyclophosphamide; MMF: mycophenolate mofetil; RTX: rituximab; SSc: systemic sclerosis; GGO: ground glass opacity; HRCT: high resolution computed tomography.

there any use in identifying these group of patients and will intervention alter the outcome and prognosis? These points shall be discussed in the following sections.

Treatment of IPAF

The most important step prior to the treatment of IPAF is confirmation of the diagnosis and then deciding on the role of immunosuppressives and/or antifibrotics. But to decide whether it is an inflammatory and/or fibrotic phenotype is the most challenging part. The idea behind grouping ILDs that have autoimmune aetiology into an umbrella term IPAF is essentially to allow for better treatment protocols and follow up. Studies have shown that IPAF has a better survival rate and fewer exacerbations when compared to IPF, but lower survival when compared to non-IPF.[27,28] ILD associated with most CTDs, barring SSc, does not have many randomised control trials and uniform treatment regimens. The most common morphological domain associated with IPAF is NSIP. The treatment options for IPAF, idiopathic NSIP and NSIP associated with CTDs are discussed below, most of which are being extrapolated to IPAF. The available evidence has been discussed in Table 2.

To conclude, there are no clear protocols for treatment of IPAF. Most patients need treatment with prednisolone with an additional immunosuppressant preferably mycophenolate mofetil (MMF) or azathioprine. Progressive disease in spite of treatment demands possibly stronger immunosuppressive agents with or without antifibrotic agents.

Table 3 Clinical features and the outcome of IPAF cohort of patients in various studies

Study/Author (Year)	Type of study (n = total subjects)	Clinical characteristics	Prognosis/survival
Ahmad K et al.[43] (2016)	Retrospective, single centre study (n = 57)	IPAF differ from IPF with increased proportion of females, predominant NSIP pattern and frequent abnormalities in NFC and MSG biopsy. Mean age of 64.4. Serologic criteria was most frequent followed by morphologic and clinical criteria. Raynaud's and inflammatory arthritis were common.	No survival benefit in comparison to IPF. Tobacco smoking had increased mortality 3/7 patients - died in the IPAF group due to infection, and were on immunosuppressive therapy. Treatment should be based on individual patients.
Oldham et al.[44] (2016)	Retrospective, single centre study (n = 144)	Mean age of 63.2 with 52.1% females. 54.2% - prior tobacco use; 54.6% - UIP pattern Raynaud's, inflammatory arthritis and mechanic hands were common. 50% of patients labelled as UCTD – ILD satisfied all the 3 domains of IPAF criteria	Survival of IPAF cohort was marginally better than IPF but worse than CTD-ILD.
Chartrand et al.[45] (2016)	Retrospective, single centre study (n = 56)	71% females with 68% never smokers. Raynaud's, distal digital fissuring, Gottron's sign and inflammatory arthritis were common. NSIP (57.1%) was common; common serologies were ANA, Anti Ro, Anti tRNA synthetase.	No deaths during the follow up period of 284.9 ± 141.3 days
Yoshimura et al.[46] (2018)	Retrospective single centre observational study (n = 32)	IPAF in comparison to CFIP were younger, with higher proportion of females, never smokers and NSIP pattern	Favourable prognosis with regard to overall survival and lesser adverse events Subgroup analysis – NSIP group significantly better survival
Dai J et al.[27] (2018)	Retrospective single centre study (n = 177)	In comparison to IPF, IPAF cohort were younger, with higher proportion of females and lower percent of ever smokers. Raynaud's and inflammatory polyarthritis were common. NSIP (61.6%) pattern was common with ANA and Anti Ro serology being frequent.	IPAF cohort had a worse survival than non-IPAF cohort. In the subgroup analysis, they concluded IPAF had better survival than IPF but worse survival than non-IPF patients.
Kelly BT et al.[47] (2018)	Retrospective single centre study (n = 101)	Male predominance, 69% of them never smokers. Frequent findings were Raynaud's phenomenon, inflammatory arthritis, ANA positivity and NSIP pattern on CT chest.	IPAF cohort had better survival in comparison to IPF, excluding those with UIP pattern on CT chest
Sambatoro et al.[48] (2019)	Prospective cohort study (n = 45)	Median age of 66 with 62.1% females. NSIP pattern, ANA positivity and Raynaud's phenomenon were the common findings	Lung disease less severe in IPAF than IPF
Lim JU et al.[49] (2019)	Prospective data collection and retrospectively reviewed (n = 54)	IPAF had lower proportion of males and ever smokers in comparison to IPF. NSIP (63%) pattern was common.	IPAF group had significant better survival than IPF and lesser episodes of ILD exacerbation.

IPAF: interstitial pneumonia with autoimmune features; IPF: idiopathic pulmonary fibrosis; ILD: interstitial lung disease; CTD-ILD: connective tissue disorder associated interstitial lung disease; NSIP: non-specific interstitial pneumonia; UIP: usual interstitial pneumonia; CFIP: chronic fibrosing interstitial pneumonia; NFC: nail fold capillaroscopy; MSG: minor salivary gland; ANA: antinuclear antibody

Prognosis and outcome

Initially, before the proposal of IPAF criteria, patients with interstitial pneumonia with autoimmune features were considered to have a better prognosis compared with IIP.[8] In 2015 Assayag et al. published a study on a cohort of 117 patients with chronic fibrosing interstitial pneumonia and applied four of the criteria that were available then (Kinder, Vij, Corte and Fischer).[42] Females constituted 40% of the cohort with a mean age of 65.5 years. The Vij and Corte criteria identified a more homogenous population due to more specific clinical and serologic criterion. IPAF patients had improved survival on univariate analysis. But after adjusting for age, gender and disease severity, only the population which met Corte criteria had improved survival. The authors concluded that survival benefit depends on the criteria used and the need for a uniform definition.[42]

Then in 2015, the European Respiratory Society/American Thoracic Society Classification criteria for IPAF was published.[8] Many studies were done by applying these criteria to their respective cohort of patients. The results of these studies including the prognosis are discussed in Table 3. Some of the studies found the IPAF cohort to have better survival in comparison to IPF. In a couple of studies, the IPAF cohort had a poor outcome in comparison to CTD-ILD and non-IPF patients. Hence, we need large prospective studies with uniform patient characteristics for comparison between the groups.

Progression of IPAF

In a retrospective study Alevizos et al. followed 50 idiopathic ILD patients who met IPAF criteria and 124 controls over a period of 5 years. They found 16% in the IPAF cohort progressed to a systemic autoimmune rheumatic disease (ARD) in comparison to 1.6% in the control group. So the patients who met IPAF criteria had 14-fold higher odds of progressing to an ARD. Female sex and the serologic domain individually and in combination confer increased risk for progression to ARD. This study reinforces the concept that IPAF criteria could help in identifying patients who are at increased risk of developing ARD.[50] In a retrospective analysis of 99 IPAF patients by Ito et al. 12.2% of patients later developed an ARD. They concluded that radiological NSIP pattern and age were poor prognostic factors for survival. They also suggested that certain autoantibodies, though specific for diagnosis of certain CTD, did not have any major role in the prognosis.[51] In view of the above studies with relatively high percentage of progression to CTD, these IPAF cohorts need to be under close follow-up.

Conclusion

IPAF is a welcome addition to the classification criteria of ILD, due to its uniformity and inclusive nature of most clinical signs and autoantibodies. With some minor revisions, this new terminology will be a clinically valid criterion, which helps clinicians to identify the group of patients with ILD who may benefit from immunosuppression therapy.

References

1 Morgenthau AS, Padilla ML. Spectrum of fibrosing diffuse parenchymal lung disease. *Mt Sinai J Med* 2009; 76: 2–23.
2 Travis WD, Costabel U, Hansell DM et al. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2013; 188: 733–48.
3 Doyle TJ, Dellaripa PF. Lung Manifestations in the Rheumatic Diseases. *Chest* 2017; 152: 1283–95.
4 Van den Hoogen F, Khanna D, Fransen J et al. 2013 Classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. *Arthritis Rheum* 2013; 65: 2737–47.
5 Mosca M, Tani C, Neri C et al. Undifferentiated connective tissue diseases (UCTD). *Autoimmun Rev* 2006; 6: 1–4.
6 Kinder BW, Shariat C, Collard HR et al. Undifferentiated connective tissue disease-associated interstitial lung disease: changes in lung function. *Lung* 2010; 188: 143–9.
7 Ferri C, Manfredi A, Sebastiani M et al. Interstitial pneumonia with autoimmune features and undifferentiated connective tissue disease: Our interdisciplinary rheumatology-pneumology experience, and review of the literature. *Autoimmun Rev* 2016; 15: 61–70.
8 Fischer A, Antoniou KM, Brown KK et al. An official European Respiratory Society/ American Thoracic Society research statement: Interstitial pneumonia with autoimmune features. *Eur Respir J* 2015; 46: 976–87.
9 Kinder BW, Collard HR, Koth L et al. Idiopathic nonspecific interstitial pneumonia: lung manifestation of undifferentiated connective tissue disease? *Am J Respir Crit Care Med* 2007; 176: 691-7.
10 Fischer A, West SG, Swigris JJ et al. Connective tissue disease-associated interstitial lung disease: a call for clarification. *Chest* 2010; 138: 251–6.
11 Vij R, Noth I, Strek ME. Autoimmune-featured interstitial lung disease: a distinct entity. *Chest* 2011; 140: 1292–9.
12 Corte TJ, Copley SJ, Desai SR et al. Significance of connective tissue disease features in idiopathic interstitial pneumonia. *Eur Respir J* 2012; 39: 661–8.
13 Bottai M, Tjärnlund A, Santoni G et al. EULAR/ACR classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups: a methodology report. *RMD Open* 2017; 3: e000507.
14 Sato S, Kuwana M, Fujita T et al. Anti-CADM-140/MDA5 autoantibody titer correlates with disease activity and predicts disease outcome in patients with dermatomyositis and rapidly progressive interstitial lung disease. *Mod Rheumatol* 2013; 23; 496–502.
15 Kang BH, Park JK, Roh JH et al. Clinical significance of serum autoantibodies in idiopathic interstitial pneumonia. *J Korean Med Sci* 2013; 28; 731–37.

16 Fischer A, Collard HR, Cottin V. "ERS/ATS Task Force on Undifferentiated Forms of Connective Tissue Disease-associated Interstitial Lung Disease". Interstitial pneumonia with autoimmune features: the new consensus-based definition for this cohort of patients should be broadened. *Eur Respir J* 2016; 47: 1295–6.
17 Katsumata Y, Kawaguchi Y, Yamanaka H. Interstitial Lung Disease with ANCA-associated Vasculitis. *Clin Med Insights Circ Respir Pulm Med* 2015; 23; 9: 51–6.
18 Tashkin DP, Elashoff R, Clements PJ et al. Scleroderma Lung Study Research Group. Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med* 2006; 354: 2655–66.
19 Tashkin DP, Roth MD, Clements PJ et al. Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. *Lancet Respir Med* 2016; 4: 708–19.
20 Hoyles RK, Ellis RW, Wellsbury J et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. *Arthritis Rheum* 2006; 54: 3962–70.
21 Elhai M, Boubaya M, Distler O et al. Outcomes of patients with systemic sclerosis treated with rituximab in contemporary practice: a prospective cohort study. *Ann Rheum Dis* 2019; 78: 979–987.
22 Silver KC, Silver RM. Management of Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD). *Rheum Dis Clin North Am* 2015; 41: 439–57.
23 Khanna D, Albera C, Fischer A et al. An Open-label, Phase II Study of the Safety and Tolerability of Pirfenidone in Patients with Scleroderma-associated Interstitial Lung Disease: the LOTUSS Trial. *J Rheumatol* 2016; 43: 1672–9.
24 Distler O, Highland KB, Gahlemann M et al. Nintedanib for systemic sclerosis–associated interstitial lung disease. *N Engl J Med* 2019; 380: 2518–28.
25 Idiopathic Pulmonary Fibrosis Clinical Research Network, Raghu G, Anstrom KJ, King TE Jr et al. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. *N Engl J Med* 2012; 366: 1968-77.
26 Wells AU, Kokosi M, Karagiannis K. Treatment strategies for idiopathic interstitial pneumonias. *Curr Opin Pulm Med* 2014; 20: 442–8.
27 Dai J, Wang L, Yan X et al. Clinical features, risk factors, and outcomes of patients with interstitial pneumonia with autoimmune features: a population-based study. *Clin Rheumatol* 2018; 37: 2125–32.
28 Lim JU, Gil BM, Kang HS et al. Interstitial pneumonia with autoimmune features show better survival and less exacerbations compared to idiopathic pulmonary fibrosis. *BMC Pulm Med* 2019; 19: 120.
29 Belloli EA, Beckford R, Hadley R et al. Idiopathic non-specific interstitial pneumonia. *Respirology* 2016; 21: 259–68.
30 Park IN, Jegal Y, Kim DS et al. Clinical course and lung function change of idiopathic nonspecific interstitial pneumonia. *Eur Respir J* 2009; 33: 68.
31 Lee JY, Jin SM, Lee BJ et al. Treatment response and long term follow-up results of nonspecific interstitial pneumonia. *J Korean Med Sci* 2012; 27: 661.
32 Swigris JJ, Olson AL, Fischer A et al. Mycophenolate mofetil is safe, well tolerated, and preserves lung function in patients with connective tissue disease-related interstitial lung disease. *Chest* 2006; 130: 30–6.
33 McCoy S, Mukadam Z, Meyer KC et al. Mycophenolate therapy in interstitial pneumonia with autoimmune features: a cohort study. *Ther Clin Risk Manag* 2018; 14: 2171–81.
34 Kondoh Y, Taniguchi H, Yokoi T et al. Cyclophosphamide and low-dose prednisolone in idiopathic pulmonary fibrosis and fibrosing nonspecific interstitial pneumonia. *Eur Respir J* 2005; 25: 528.
35 Corte TJ, Ellis R, Renzoni EA et al. Use of intravenous cyclophosphamide in known or suspected, advanced non-specific interstitial pneumonia. *Sarcoidosis Vasc Diffuse Lung Dis* 2009; 26: 132.
36 Maher TM, Corte TJ, Fischer A, et al. Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: design of a double-blind, randomised, placebo-controlled phase II trial. *BMJ Open Respir Res* 2018; 5: e000289. doi:10.1136/ bmjresp-2018-000289.
37 Flaherty KR, Brown KK, Wells AU et al. Design of the PF-ILD trial: a double-blind, randomised, placebo-controlled phase III trial of nintedanib in patients with progressive fibrosing interstitial lung disease. *BMJ Open Respir Res* 2017; 4: e000212. doi: 10.1136/bmjresp-2017-000212.
38 Huang H, Sun YX, Li S et al. The clinical experience of pirfenidone based on corticosteroids and immunosuppressant treatment for interstitial pneumonia with autoimmune features. *Zhonghua Jie He He Hu Xi Za Zhi*. 2019 12; 42: 700–4.
39 Sharp C, McCabe M, Dodds N et al. Rituximab in autoimmune connective tissue disease-associated interstitial lung disease. *Rheumatology (Oxford)* 2016; 55: 1318–24.
40 Kurita T, Yasuda S, Amengual O et al. The efficacy of calcineurin inhibitors for the treatment of interstitial lung disease associated with polymyositis/dermatomyositis. *Lupus* 2015; 24: 3–9.
41 Vacchi C, Sebastiani M, Cassone G et al. Therapeutic Options for the Treatment of Interstitial Lung Disease Related to Connective Tissue Diseases. A Narrative Review. *J Clin Med* 2020; 9: 407.
42 Assayag D, Kim EJ, Elicker BM et al. Survival in interstitial pneumonia with features of autoimmune disease: a comparison of proposed criteria. *Respir Med* 2015; 109: 1326–1.
43 Ahmad K, Barba T, Gamondes D et al. Interstitial pneumonia with autoimmune features: clinical, radiologic, and histological characteristics and outcome in a series of 57 patients. *Respir Med* 2017; 123: 56–62.
44 Oldham JM, Adegunsoye A, Valenzi E et al. Characterisation of patients with interstitial pneumonia with autoimmune features. *Eur Respir J* 2016; 47: 1767–75.
45 Chartrand S, Swigris JJ, Stanchev L et al. Clinical features and natural history of interstitial pneumonia with autoimmune features: a single centre experience. *Respir Med* 2016; 119: 150– 4.
46 Yoshimura K, Kono M, Enomoto Y et al. Distinctive characteristics and prognostic significance of interstitial pneumonia with autoimmune features in patients with chronic fibrosing interstitial pneumonia. *Respir Med* 2018; 137: 167–75.
47 Kelly BT, Moua T. Overlap of interstitial pneumonia with autoimmune features with undifferentiated connective tissue disease and contribution of UIP to mortality. *Respirology* 2018; 23: 600–5.
48 Sambataro G, Sambataro D, Torrisi SE et al. Clinical, serological and radiological features of a prospective cohort of Interstitial Pneumonia with Autoimmune Features (IPAF) patients. *Respir Med* 2019; 150: 154–60.
49 Lim JU, Gil BM, Kang HS et al. Interstitial pneumonia with autoimmune features show better survival and less exacerbations compared to idiopathic pulmonary fibrosis. *BMC Pulm Med* 2019; 19:120.
50 Alevizos MK, Giles JT, Patel NM et al. Risk of progression of interstitial pneumonia with autoimmune features to a systemic autoimmune rheumatic disease. *Rheumatol.* 2020; 59: 1233–1240.
51 Ito Y, Arita M, Kumagai S et al. Serological and morphological prognostic factors in patients with interstitial pneumonia with autoimmune features. *BMC Pulm Med* 2017; 17: 111.