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PERSPECTIVE

International consensus statement on idiopathic pulmonary fibrosis

U. Costabel*, T.E. King#

In the new millennium, idiopathic pulmonary fibrosis (IPF) is not what it was thought to be 20 years ago. In the past, the term was used for a heterogeneous group of interstitial lung disorders of unknown cause, after exclusion of possible exposures or associated conditions. Now IPF is more narrowly defined as a distinct clinical entity, with certain characteristic clinical, radiological and morphological features; specifically, the pattern of usual interstitial pneumonia (UIP) on surgical lung biopsy [1]. Historically, several histopathological subsets of the family of the idiopathic interstitial pneumonias were considered part of the spectrum of IPF (or cryptogenic fibrosing alveolitis (CFA), the preferred term in the British literature). The Liebow classification of 1969, divided the idiopathic interstitial pneumonias into several histological subsets: usual interstitial pneumonia (UIP), desquamative interstitial pneumonia (DIP), bronchiolitis obliterans with interstitial pneumonia (BIP), lymphoid interstitial pneumonia (LIP), and giant cell interstitial pneumonia (GIP). LIP and GIP were dropped from this classification because many of the former cases were found to be lymphoproliferative disorders and many of the latter were cases of hard metal pneumoconiosis. Recently, KATZENSTEIN and MYERS [2] proposed that the entities acute interstitial pneumonia (AIP or diffuse alveolar damage of unknown aetiology) and nonspecific interstitial pneumonia (NSIP) be added to the spectrum of idiopathic interstitial pneumonia. Furthermore, the specific features of the UIP pattern have been more clearly defined, allowing for better separation of this lesion from the other patterns, particularly NSIP. The major reason for separating IPF/UIP, the most common idiopathic interstitial pneumonia, from the other entities, was the increasingly reported severe prognosis in the IPF/UIP subset compared to the other subgroups of the idiopathic interstitial pneumonias. Median survival for the more narrowly defined IPF patients is now only 2.8 yrs, compared to approximately 5 yrs in previous studies, which often included cases with NSIP and DIP patterns on lung biopsy or were clinical diagnoses [3–5].

In early 2000, guidelines were published for the diagnosis and management of IPF by the American Thoracic Society (ATS), European Respiratory Society (ERS) and American College of Chest Physicians (ACCP), which took these new developments into consideration [1]. This editorial will highlight the key issues and conclusions from this consensus report for the ERJ readers and ERS members. The level of evidence for the recommendations is largely that of expert opinion developed by consensus. There is no supportive evidence from well conducted randomised controlled trials. The following is a summary of this consensus statement.

Key conclusions or recommendations from the panel of experts included the following:

1. UIP is the histopathological pattern that identifies patients with IPF. Other patterns such as DIP, respiratory bronchiolitis-associated interstitial lung disease (RBILD), NSIP, LIP, AIP, and idiopathic bronchiolitis obliterans organising pneumonia (idiopathic BOOP) are considered separate entities and are to be excluded from the group of patients with IPF.

2. Clinical criteria are specified for determining the presumptive diagnosis of IPF and distinguishing IPF from other diffuse parenchymal lung diseases.

3. Surgical lung biopsy is recommended in most patients, especially those with suspected IPF who have clinical, physiological, or radiological features that are not typical for IPF and who are without contraindications to surgery. A major purpose is to distinguish UIP from other subsets of the idiopathic interstitial pneumonia that have a better response to available treatment.

4. No data exist that adequately document that any of the current treatment approaches improves survival or the quality of life for patients with IPF.

5. The committee suggests that therapy is not indicated for all patients with IPF. If therapy is recommended to a patient, it should be started at the first identification of clinical or physiological evidence of impairment or documentation of decline in lung function.

6. A combination of clinical, radiographical, and physiological parameters should be used to assess the clinical course and response to treatment of IPF.

7. Lung transplantation should be considered for those patients who experience progressive deterioration

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Committee Members: T.E. King (chairman), U. Costabel, J.F. Cordier, G.A. DoPico, R.M. Du Bois, D. Lynch, J. Myers, R. Panos, G. Raghu, D. Schwartz, C.M. Smith.

*Ruhrlandklinik, Dept Pneumology/Allergy, Tüschener Weg 40, 45239, Essen, Germany and #Medical Services, San Francisco General Hospital, 1001 Potrero Avenue Room 5H22, San Francisco CA 94110, USA.

Correspondence: Ulrich Costabel, Ruhrlandklinik, Dept Pneumology/Allergy, Tüschener Weg 40, 45239, Essen, Germany. Fax: 49-2014334029.

Table 1. – Criteria for a clinical diagnosis of idiopathic pulmonary fibrosis

Major criteria
1) Exclusion of other known causes of ILD, such as certain drug toxicities, environmental exposures, and connective tissue diseases
2) Abnormal pulmonary function studies that include evidence of restriction and impaired gas exchange
3) Bibasilar reticular abnormalities with minimal ground glass opacities on HRCT
4) Transbronchial lung biopsy or bronchoalveolar lavage showing no features to support an alternative diagnosis
Minor criteria
1) Age >50 yrs
2) Insidious onset of otherwise unexplained dyspnoea on exertion
3) Duration of illness $\geqslant 3$ months
4) Bibasilar, inspiratory crackles (dry or "Velcro" type)

All four major and three of four minor criteria must be present. ILD: interstitial lung disease; HRCT: high-resolution computed tomography.

and who meet the established criteria for lung transplantation.

8. A multicentre, international consortium should be established to determine the natural history and optimal treatment strategy for the management of patients with IPF.

The new definition of IPF given in this statement reads as follows: "IPF is a specific form of chronic fibrosing interstitial pneumonia, limited to the lung, and associated with the histologic appearance of UIP on surgical (thoracoscopic or open) lung biopsy". The aetiology is unknown. The definite diagnosis of IPF in the presence of a surgical biopsy showing UIP includes the following. 1. Exclusion of other known causes of interstitial lung disease such as drug toxicities, environmental exposures, and collagen vascular diseases. 2. Abnormal pulmonary function studies that include evidence of restriction and/or impaired gas exchange. 3. Abnormalities on conventional chest radiographs or high-resolution computed tomography (HRCT).

Although in the absence of a surgical lung biopsy, the diagnosis of IPF remains uncertain, the committee specified clinical criteria for determining the presumptive diagnosis of IPF. In the immunocompetent adult, the presence of all four major diagnostic criteria and at least three of the four minor criteria increases the likelihood of a correct clinical diagnosis of IPF (table 1).

The epidemiology of IPF remains problematic since the precise incidence and prevalence are not known. Previous estimates of prevalence (3 – 6 cases per 100,000 in the general population) have increased markedly in a more recent population-based study in New Mexico, USA, which revealed a prevalence of 20 cases per 100,000 for males and 13 cases per 100,000 for females. However, the criteria for IPF that provided the basis for these data are not precisely defined, and likely different from the strict new criteria of this statement. Patients with IPF are usually 40 – 70 yrs of age. Approximately two-thirds of patients with IPF are over the age of 60 yrs at the time of presentation, with a mean age at diagnosis of 66 yrs. The incidence of the disease increases with older age. In this regard, it is important to know that patients younger than 50 yrs at diagnosis are more likely to have one of the other histopathological subsets of idiopathic interstitial pneumonia associated with a better prognosis. Risk factors for IPF include cigarette smoking and environmental factors such as metal dust and wood dust exposure.

The diagnostic approach in IPF includes thorough and extensive medical history and physical examinations, performance of chest radiograph and HRCT, assessment of pulmonary function and laboratory tests, routine use of transbronchial biopsy or bronchoalveolar lavage (BAL) to exclude features to support an alternative diagnosis, and finally surgical lung biopsy, particularly in those who do not fulfil the diagnostic criteria shown in table 1.

Medical history and physical examination

IPF usually presents insidiously, with gradual onset of progressive dyspnoea on exertion and a nonproductive cough, usually present for more than 6 months before presentation. The most frequent clinical signs are bibasilar, end-inspiratory fine crackles on auscultation in more than 80% of patients (typically "dry" and "Velcro" in quality), and digital clubbing in up to 50% of patients. Extrapulmonary involvement does not occur, but weight loss, malaise and fatigue may be noted. Fever is rare, in contrast to older series, and its presence suggests an alternative diagnosis, such as BOOP, extrinsic allergic alveolitis, or NSIP.

Pulmonary function and laboratory tests

The typical findings of pulmonary function tests are restriction and impaired gas exchange. Elevation of serum lactate dehydrogenase (LDH) levels may be noted, but is a nonspecific finding; antinuclear antibodies or rheumatoid factor occur in 10 – 20% of cases. Rarely, patients with clinical features of IPF may later develop a defined connective tissue disease. In these cases, the term IPF is not maintained.

High-resolution computed tomography scanning

This technique has changed the diagnostic evaluation of patients with IPF. HRCT allows earlier diagnosis of IPF, helps to narrow the differential diagnosis based on the computed tomography (CT) pattern, and allows the identification of associated emphysema. The HRCT pattern of IPF commonly shows patchy, predominantly

peripheral, subpleural, bibasal reticular abnormalities, often with associated traction bronchiectasis and bronchiolectasis and/or subpleural honeycombing in areas of more severe involvement. Ground glass opacities are usually limited in extent and commonly progress to reticular opacification with subsegment honeycombing. The accuracy of a confident diagnosis of IPF made on HRCT by a trained observer appears to be about 90%. Such confident diagnosis is made in about two-thirds of patients with histological UIP. Extensive ground glass opacity on CT of the lung (>30% of the lung is involved) should prompt consideration of another diagnosis rather than IPF, particularly DIP, but also RBILD, hypersensitivity pneumonitis, idiopathic BOOP, or NSIP.

Bronchoalveolar lavage and transbronchial biopsy

The pattern of inflammatory cells in BAL may be helpful in narrowing the differential diagnosis, but is not diagnostic of IPF. Patients with IPF typically have elevated BAL neutrophils and eosinophils, but these findings are also observed in other fibrosing lung conditions. A lone increase in lymphocytes is uncommon in IPF, and when present, another disorder should be excluded (*e.g.* granulomatous infectious disease, sarcoidosis, hypersensitivity pneumonitis, idiopathic BOOP, NSIP, or LIP). The same is true for transbronchial biopsy, which cannot be used to diagnose UIP but is useful to exclude IPF, by showing an alternative specific diagnosis (*e.g.* malignancy, infections, sarcoidosis, hypersensitivity pneumonitis, BOOP, eosinophilic pneumonia, or histiocytosis X).

Histopathological assessment on surgical lung biopsy

UIP is the pathological abnormality essential to the diagnosis of IPF. The histological hallmark and the chief diagnostic criterion is a heterogeneous appearance with alternating areas of normal lung, interstitial inflammation, fibrosis, and honeycomb change. Smooth muscle hyperplasia is commonly seen in areas of fibrosis and honeycomb change. The distribution of fibrosis is frequently subpleural, peripheral, and paraseptal. Scattered fibroblast foci present at the junction of fibrosis with normal lung are a consistent finding. A histopathological pattern of UIP is not specific for IPF but can occur in patients with asbestosis, connective tissue disease, chronic hypersensitivity pneumonitis and certain drug-induced lung diseases. In this regard, the new dogma is: "All IPF is UIP, but on the other hand, not all UIP is IPF".

Treatment

The current conventional treatment options and potential alternative treatments including novel agents are thoroughly reviewed and discussed in the statement. The conclusion was that, to date, we lack sufficient clinical evidence that any treatment improves survival or the quality of life for patients with IPF. Despite the ubiquitous use of corticosteroids, no prospective, randomized, double-blind, placebo-controlled trial has evaluated the efficacy of corticosteroids in the treatment of IPF. The disappointing results of treatment with anti-inflammatory agents have led to the study of alternative therapeutic strategies, including antifibrotic agents such as cholchicine, D-penicillamine, interferon-γ, interferon-β, and pirfenidone, or antioxidants such as *N*-acetylcysteine, but their usefulness remains to be proven.

Given the poor prognosis for a patient with IPF, many experts have recommended that treatment be initiated in all patients with IPF who do not have contraindications to therapy. The committee believes that therapy is not indicated for all patients. Importantly, given the limited success of current treatments, the potential benefits of any treatment protocol of an individual patient with IPF, may be outweighed by increased risk for treatment-related complications. The exact time that therapy should be started is unknown. The committee believes that response rates may be higher when treatment is initiated early in the course of disease, before irreversible fibrosis has developed. Therefore, the committee recommends that if therapy will be offered to a patient, it should be started at the first identification of clinical or physiological evidence of impairment or documentation of decline in lung function.

The current recommendation for therapy by the committee is summarized in table 2. It is a combined therapy (corticosteroids and either azathioprine or cyclophosphamide) for those patients who have been adequately informed and who possess features consistent with a more likely favourable outcome (see table 3). This recommendation is based on two studies involving a small number of patients, one study on cyclophosphamide, one on azathioprine, which suggest that the addition of either of these drugs to modest doses of corticosteroids may offer a small benefit over the steroids alone.

Regarding the length of therapy, combined therapy should be continued for at least 6 months. The patients should be evaluated every 3–6 months. The therapy should be continued indefinitely only in individuals with objective evidence of continued improvement or stabilisation.

A favourable (or improved) response to therapy is defined by two or more of the following on two consecutive visits over a 3–6 months period: 1) symptoms decreased (dyspnoea or cough); 2) radiology improved (reduced parenchymal abnormalities); 3) physiology improved by two or more parameters (⩾10% increase in total lung capacity or forced vital capacity, ⩾15% increase in the carbon monoxide diffusing pattern of the lung, significant improvement (⩾4%, ⩾4 mmHg) or normalization of O_2 saturation or P_{a,O_2} during exercise).

Other management issues such as monitoring for adverse effects of treatment, a physiological rehabilitation program, supplemental oxygen therapy, treatment of severe paroxysms of cough, and lung transplantation are also addressed in the statement.

In the final section on limitations and future goals it is mentioned that the data on the full spectrum of cases

Table 2. – Current treatment recommendations for idiopathic pulmonary fibrosis

Corticosteroid (prednisone or equivalent)
0.5 mg·kg^{-1} lean body weight (LBW)·day^{-1} orally for 4 weeks
0.25 mg·kg^{-1}·day^{-1} for 8 weeks
Taper to 0.125 mg·kg^{-1}·day^{-1} or 0.25 mg·kg^{-1} on alternate days
plus
Azathioprine
2 – 3 mg·kg^{-1} LBW·day^{-1}
Maximum dose 150 mg daily
Dosing should begin at 25 – 50 mg·day^{-1}, increasing by 25 mg increments every 1 – 2 weeks until the maximum dose is achieved
or
Cyclophosphamide
2 mg·kg^{-1} LBW·day^{-1}
Maximum dose 150 mg daily
Dosing should begin at 25 – 50 mg·day^{-1}, increasing by 25 mg increments every 1 – 2 weeks until the maximum dose is achieved

Table 3. – Indicators of longer survival among idiopathic pulmonary fibrosis patients

1) Younger age ($<$50 yr)
2) Female sex
3) Shorter symptomatic period ($\leqslant$1 yr) with less dyspnoea, relatively preserved lung function
4) Presence of ground glass and reticular opacities on HRCT
5) Increased proportion of lymphocytes (20 – 25 %) in BAL fluid
6) A beneficial response or stable disease 3 – 6 months after initial corticosteroid therapy
7) A history of "current" cigarette smoking at the time of diagnosis has been associated with improved survival – this finding remains unexplained

of IPF are limited. More knowledge about the epidemiology and genetic predisposition to IPF is needed. Furthermore, prospective and controlled studies with diverse immunosuppressive or antifibrotic agents in the treatment of IPF are required. Owing to the rarity of IPF, this will require a large number of clinical centres. Thus, the committee strongly recommends the establishment of a multicentre, international consortium to allow the recruitment of sufficient numbers of subjects needed to determine the optimal treatment strategy for IPF.

The personal conclusions from the IPF statement can be summarized as follows.

The recent development of a new clinicoradiologic and pathologic classification of the idiopathic interstitial pneumonias has changed the concept of IPF. This term is now exclusively reserved for patients with the key histologic feature of UIP, the most common idiopathic interstitial pneumonia. Other subgroups with a better prognosis (DIP/RBILD, NSIP, idiopathic BOOP) or a worse prognosis (AIP) are now considered separate entities. In this regard, there is still a certain nomenclature dilemma: "All IPF is UIP, but not all UIP is IPF". The diagnosis of IPF requires the exclusion of other diseases which may show a UIP-like pattern, mainly asbestosis, drug toxicities, and collagen vascular disease.

In the absence of surgical lung biopsy, newly proposed major and minor clinical criteria facilitate the presumptive diagnosis of IPF. HRCT scanning is particularly valuable in recognizing the UIP pattern, and allowing the differentiation of UIP from other interstitial lung disorders. Careful attention to technique and evaluation by an experienced radiologist are necessary to assure diagnostic accuracy. If clinical presentation and/or HRCT pattern is not characteristic for IPF, the diagnosis can only be accepted with the help of surgical lung biopsy.

Given the clear importance of a confident diagnosis in determining possible treatment and defining the prognosis, when indicated, surgical lung biopsy should be obtained early in the course of the illness or before commencement of treatment. Clinicians who do not have access to the option of pathologists experienced in examining lung biopsies of patients with idiopathic interstitial pneumonia should refer these samples to other centres for additional evaluation.

Some of the previously defined prognostic factors may not be relevant for patients with IPF/UIP as currently defined. Examples are younger age (more likely DIP or NSIP patients in the older series), cigarette smoking (likely DIP or RBILD patients in the older series), or a BAL lymphocytosis (likely NSIP patients).

In future therapeutic trials with novel agents, the patient populations should be as homogeneous as possible. In this regard, the recruited patients should strictly fulfil the clinical criteria for the diagnosis as outlined in the statement. In addition, when populations are randomized in controlled clinical trials, it is important to consider stratification according to the various prognostic factors. Since a placebo group without any immunosuppressive treatment is hardly justified, it is suggested to use the current treatment recommendation (table 2) as standard therapy in future trials, to which either the investigative drug or placebo is added or compared.

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