Review Article

Access this article online

Quick Response Code:

Website: www.eurasianjpulmonol.com

DOI: 10.4103/ejop.ejop_45_19

Idiopathic pulmonary fibrosis: What has changed in the diagnosis and treatment from past to present?

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Abstract:

Idiopathic pulmonary fibrosis (IPF) is the most common and most fatal of all lung diseases that cause widespread scarring in the lungs. High-resolution computed tomography (HRCT) has high diagnostic value in the diagnosis of IPF. Patients exhibiting a pattern of usual interstitial pneumonia (UIP) can be diagnosed with IPF without the need for a biopsy if no other conditions exist that could cause this pattern. If no pattern of UIP exists, a multidisciplinary council should gather to discuss the HRCT and pathological and clinical findings and to decide upon a diagnosis. Appropriate supportive therapies such as oxygen therapy, pulmonary rehabilitation, and seasonal flu and pneumococcal vaccines should be included in the management of the disease. Comorbidities must be investigated and treated. There have been studies identifying the benefits of pirfenidone and nintedanib in patients with mild-to-moderate IPF. There is a lack of appropriate data to guide the selection between pirfenidone and nintedanib, and the patient's preferences and drug tolerance must be considered when making such a drug selection. There have been no randomized studies to date showing the benefits of drugs in severe IPF. The prevention of acid reflux may be beneficial, but the symptoms are obscure. Lung transplantation can be an option for young patients with a severe and progressive disease when there are no comorbidities to pose a contraindication.

Keywords:

Comorbidity, diagnosis, idiopathic pulmonary fibrosis, treatment

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Received: 28-05-2019
Revised: 06-06-2019
Accepted: 15-07-2019
Published: 30-04-2020

Introduction

Idiopathic pulmonary fibrosis (IPF) refers to a prototype of chronic, progressive, and diffuse parenchymal lung diseases that are associated with significant mortality and morbidity. It is a form of chronic interstitial pneumonia with an unknown cause that has a course of progressive fibrosis. IPF is defined as the presence of a histopathological and radiological appearance confined to the lungs and consistent with usual interstitial pneumonia (UIP) in patients of advanced age (>50 years).[1,2] Mean survival following diagnosis is approximately 3 years, and the most formidable finding is that an approximately 5% increase is observed in prevalence every year.[3] The mortality rate associated with IPF currently exceeds that of many cancer types. The approach to diagnosis and treatment of IPF has evolved over time, although a multidisciplinary approach to diagnosis still maintains importance. This manuscript compares the current guidelines published on the

How to cite this article: Anar C, Okutan O, Şengül A, Yazici O, Altinsoy B. Idiopathic pulmonary fibrosis: What has changed in the diagnosis and treatment from past to present? Eurasian J Pulmonol 2020;22:1-16.

diagnosis and treatment of IPF (ATS/ERS/JRS/ALAT 2018, Germany 2017, Switzerland 2017, Japan 2017, and France 2013) and discusses their recommendations.

Serology and radiological investigations hold an important place in the diagnosis of the disease. Histopathological sampling is required particularly in patients who lack clear radiological characteristics. The present manuscript reviews the above-mentioned guidelines under these headings and scrutinizes their most notable features and differences.

Radiology

The main examination method suggested in IPF diagnosis algorithms in the international guidelines is high-resolution computed tomography (HRCT). The UIP pattern on HRCT is characterized by basal, peripheral, and subpleural reticular opacities, often accompanied by traction bronchiectasis and a honeycomb appearance.[4]

In 2011, ATS, ERS, JRS, and ALAT published a joint report dividing HRCT UIP pattern criteria into three categories (UIP pattern, possible UIP pattern, and inconsistent with UIP pattern), whereas the HRCT UIP pattern criteria were divided into four different categories in 2018 (UIP pattern, possible UIP pattern, indeterminate UIP pattern, and alternative diagnosis)[5] [Tables 1 and 2]. In the two guidelines, reticular densities, honeycomb appearance (± traction bronchiectasis), predominant involvement of subpleural and basal areas, and a lack of inconsistent findings with UIP were defined as different UIP patterns. In the guidelines published in 2011, subpleural and basal predominance together with reticular opacities and the presence of findings inconsistent with UIP were noted for possible UIP patterns, whereas in the most recent ATS/ERS/JRS/ALAT 2018 guidelines, it was predicated that subpleural and basal predominance must be accompanied not only by reticular opacity but also by certain traction bronchiectasis/bronchiolectasis.[4,5]

Table 1: High-resolution computed tomography criteria for the usual interstitial pneumonia pattern (2011 ATS/ERS/JRS/ALAT)[4]

UIP pattern (all 4 characteristics)	Possible UIP pattern (all 3 characteristics)	Not consistent with the UIP pattern (any of the 7 characteristics)
Subpleural, basal predominance	Subpleural, basal predominance	Upper- and mid-zone predominance
Reticular opacities	Reticular opacities	Peribronchovascular predominance
Honeycomb appearance alone or together with traction bronchiectasis	Presence of features that are inconsistent with the UIP pattern	Diffuse ground-glass opacities
Presence of features that are inconsistent with the UIP pattern		Diffuse micronodular
		Atypical cysts
		Low-mosaic attenuation
		Segmental/lobar consolidation

UIP: Usual interstitial pneumonia

Table 2: Imaging patterns in high-resolution computed tomography (ATS/ERS/JRS/ALAT 2018)

UIP	Possible UIP	Indeterminate (inconsistent UIP)	Alternate diagnoses
Subpleural and basal predominance; often heterogeneous distribution*	Subpleural and basal predominance; often heterogeneous distribution	Subpleural and basal predominance	Findings suggestive of another diagnosis
			CT characteristics
			Cysts
Honeycombing with or without peripheral traction bronchiectasis or bronchiolectasis	Reticular pattern with peripheral traction bronchiectasis or bronchiolectasis	Subtle reticulation; may have mild ground-glass opacities or distortion ("early UIP pattern")	Mosaic attenuation
			Predominant ground-glass
	May have mild ground-glass opacities	CT features and/or a distribution of lung fibrosis that does not suggest a specific etiology ("truly indeterminate for UIP")	Micronodular
			Centrilobular nodules
			Consolidation
			Predominant distribution
			Perilymphatic
			Peribronchovascular
			Upper and mid zone
			Other
			Pleural plaque (asbestosis)
			Dilated esophagus (CTDs)
			Lymph node enlargement (other etiologies)
			Pleural effusion, pleural thickening (CTDs, drugs, etc.)

*Variants of distribution: Occasionally diffuse, may be asymmetrical. CT: Computed tomography, UIP: Usual interstitial pneumonia, CTDs: Collagen tissue disease

Contrasting the 2011 guidelines, a new group entitled indeterminate/suspected was added to the possible UIP patterns [Table 2]. Findings that are inconsistent with UIP often point to other interstitial diseases, including a predominant involvement of the upper and middle zones, diffuse ground-glass opacities (different from reticular densities), vast amounts of micronodules (bilateral, more in the upper zones), discrete cysts (multiple, distant from the honeycombing), diffuse mosaic patterns and air trapping (bilateral, in three or more lobes), and consolidation. The HRCT findings grouped under the category of "findings inconsistent with UIP" in previous guidelines were brought under an "alternative diagnosis" heading in the ATS/ERS/JRS/ALAT 2018 guidelines [Table 2].

Physiological Tests, Serology, and Genetic Analyses

Although physiological tests are not required for a diagnosis of IPF in the ATS/ERS/JRS/ALAT guidelines, some parameters (i.e., DLCO <40%) and changes in forced vital capacity (FVC) are predictive of mortality and disease progression.[1] The German guidelines state a 10% or greater decline in FVC in pulmonary function or a decrease in Diffusion capacity (DLCO) together with FVC decline, low arterial blood gases, or the results of 6-min walk test (6-MWT). In such cases, an evaluation should be made of all clinical symptoms (dyspnea and cough) to determine disease progression and prognosis rather than assuming a diagnosis and treatment of IPF.[6] The French guidelines use a score based on the combination of symptoms (severity of dyspnea) and the results of pulmonary function tests (FVC and DLCO), 6-MWT, intensity of honeycombing on HRCT, and pulmonary hypertension (PH) detected on echocardiography to evaluate prognosis.[7] All of the international guidelines recommend serologic tests be performed at the time of diagnosis, as connective tissue diseases cause interstitial lung disease (ILD) and even histopathological UIP patterns.[5-8] Furthermore, a diagnosis of IPF requires the exclusion of other ILDs. For this reason, the ATS/ERS/JRS/ALAT 2018 guidelines report that serologic tests should be routine in all patients with newly diagnosed ILD, although there is still a lack of consensus on which serologic tests are necessary. The majority of panelists, however, emphasized the importance of testing for C-reactive protein levels, erythrocyte sedimentation rate, antinuclear antibodies (by immunofluorescence), rheumatoid factor, myositis panel, and anticyclic

Table 3: Comparison of 2011 and 2018 ATS guidelines in the diagnosis of idiopathic pulmonary fibrosis

	2018 ATS/ERS/JRS/ALAT		2011 ATS/ERS/JRS/ALAT
	Probable UIP, indeterminate UIP and alternative diagnoses according to the HRCT pattern	HRCT pattern of UIP	Patients not classified according to the HRCT pattern
Cellular analysis of BAL fluid	Recommended	Not recommended	Not recommended diagnostic workup of patients with IPF, may be performed in a very small portion
Surgical lung biopsy	Recommended	Not recommended (strong recommendation)	Surgical lung biopsy not required in patients with an HRCT pattern consistent with UIP
Transbronchial biopsy	No recommendation made for or against a transbronchial lung biopsy	Transbronchial lung biopsy not recommended (strong recommendation)	Transbronchial lung biopsy should not be made in the majority of the patients for the investigation of IPF, but may be appropriate in the minority
Cryobiopsy	No recommendation made for or against cryobiopsy	Cryobiopsy not recommended (strong)	Not addressed
Taking a history of drug use and environmental exposure	We recommend taking a detailed history of both medication use and environmental exposure at home, work and other places the patient visited frequently to exclude potential causes of interstitial lung diseases		Diagnosis of IPF requires the exclusion of other known causes of interstitial lung diseases (e.g., domestic and occupational environmental exposure, connective tissue disease, and drug toxicity)
Use of serological testing to exclude connective tissue diseases	Serological testing is recommended to exclude connective tissue diseases as potential causes of interstitial lung diseases		Diagnosis of IPF requires the exclusion of other known causes (e.g., domestic and occupational environmental exposure, connective tissue disease, and drug toxicity)
Multidisciplinary Approach	Multidisciplinary discussion is recommended to make a decision		Multidisciplinary discussion is advised to evaluate for IPF
Serum Biomarkers	The measurement of serum MMP-7, SPD, CCL-18 or KL-6 levels is not recommended to distinguish IPF from other interstitial lung diseases (strong)		Not addressed

BAL: Bronchoalveolar lavage, UIP: Usual interstitial pneumonia, HRCT: High-resolution computed tomography, IPF: Idiopathic pulmonary fibrosis, SPD: Surfactant protein D, MMP-7: Matrix metalloproteinase-7, KL-6: Krebs von den Lungen-6, CCL-18: CC-chemokine ligand 18

citrullinated peptide. Other comprehensive tests should be based on the relevant symptoms and signs on a patient-to-patient basis[5] [Table 3].

The ATS/ERS 2018 guidelines recommend against the measurement of matrix metalloproteinase-7, surfactant protein D, or Krebs von den Lungen-6 when differentiating IPF from other ILDs in patients with a newly detected unknown ILD, but suspected of having IPF, whereas the 2011 guidelines do not address this issue [Table 3].

The ATS/ERS/JRS/ALAT 2018 guidelines do not recommend genetic screening for patients with IPF,[4] although several associations have been identified between IPF and genetic mutations or polymorphisms. Some genetic variants are associated with increased or decreased survival and may predict disease outcomes,[9,10] and knowledge of these genetic markers may affect the timing of referral to a lung transplant center. Genetic counseling may also help in describing familiar forms of fibrosis. In addition, polymorphisms such as TOLLIP mutations may affect responses to specific therapies such as N-acetylcysteine (NAC) therapy.[11] The German guidelines have not yet recommended routine genetic screening.[6] The Swiss guidelines recommend genetic testing for gene mutations when familial fibrosis is suspected or if IPF is detected at a young age (>50 years). The Swiss guidelines also state that routine screening for genetic polymorphisms (i.e., MUC5B) is not recommended at this time.[8]

Bronchoalveolar Lavage and Biopsy (Transbronchial Biopsy, Cryobiopsy, and Surgical Biopsy)

Bronchoalveolar lavage (BAL) is one of the available invasive diagnostic methods. The ATS/ERS 2018 guidelines reviewed eight studies involving a BAL analysis.[12-19] In the studies, neutrophil, lymphocyte, eosinophil, and macrophage counts in the BAL fluid of patients with IPF were compared with the findings of a cellular BAL fluid analysis of patients with other ILDs, such as hypersensitivity pneumonia, sarcoidosis, eosinophilic pneumonia, nonspecific interstitial pneumonia (NSIP), and lymphocytic interstitial pneumonia (LIP). The mean lymphocyte count in the BAL fluid of patients with IPF ranged between 7.2% and 26.7%, which are lower levels than those in patients with NSIP, sarcoidosis, and LIP. The percentage of lymphocytes in BAL fluid was higher than that in patients with respiratory bronchiolitis-related ILD (RB-ILD), whereas no difference was identified when compared to patients with hypersensitivity pneumonia or eosinophilic pneumonia. The mean eosinophil count in the BAL fluid of patients with IPF ranged between 2.39% and 7.5%, showing higher levels than in patients with eosinophilic pneumonia. No significant difference was found when patients with IPF were compared to patients with NSIP, hypersensitivity pneumonia, organized pneumonia, sarcoidosis, RB-ILD, or LIP in terms of eosinophil counts in the BAL fluid. The mean neutrophil count in the BAL fluid of patients with IPF ranged between 5.9% and 22.08%, showing higher levels than in patients with hypersensitivity pneumonia, cellular NSIP, eosinophilic pneumonia, and LIP. No significant difference was reported between patients with IPF and those with fibrotic NSIP, cryptogenic organized pneumonia, or sarcoidosis in terms of neutrophil count.[12-19] As a result of these findings, the authors of the guidelines concluded that the estimated differences in the cellular composition of BAL fluid in patients with IPF are of low reliability when compared to cellular BAL analyses of patients with other ILDs. This led them to state that BAL should be avoided in patients exhibiting radiological patterns of definitive UIP, but that it can be conditionally recommended in patients with possible, indeterminate, and alternative diagnosis patterns. Although the ATS/ERS/JRS/ALAT guidelines for the diagnosis and treatment of IPF do not recommend the routine use of BAL analysis, it must be kept in mind that an analysis of BAL fluid may guide a differential diagnosis of lung malignancies, lymphoma, eosinophilic pneumonia, chronic hypersensitivity pneumonia, and asbestos exposure that can be confused with idiopathic interstitial pneumonias.[2] On the other hand, the German IPF guidelines make no recommendation of routine BAL fluid analyses.[6] The French guidelines recommend BAL in suspected IPF, particularly if HRCT does not show a definitive UIP pattern.[7] The Swiss guidelines recommend BAL in patients with suspected IPF, particularly to investigate other possible causes of fibrotic diseases, such as chronic hypersensitivity pneumonia and fibrotic NSIP.[8]

Transbronchial biopsy, cryobiopsy, and surgical biopsy are other invasive diagnostic methods. The ATS/ERS/JRS/ALAT 2018 guidelines reviewed seven studies that used transbronchial biopsy for the establishment of a histopathological diagnosis.[20-26] These studies involved study populations that included patients with ILDs of unknown cause and those with UIP pattern on HRCT and revealed that transbronchial biopsy yielded a sufficient amount of analysis sample in roughly three-quarters of patients (640 out of 825 patients in five studies, 77.6%; 95% confidence interval [CI], 74.6%–80.3%). Among the adequate samples, a diagnosis could be reached in approximately half of the patients (409 out of 948 in seven studies, 43.1%; 95% CI, 40.0%–46.3%) and a small majority could not be classified (539 out of 948 patients in seven studies,

56.9%; 95% CI, 53.7%–60.0%). It was suggested that only one-third of all transbronchial biopsies lead to a specific diagnosis (409 out of 1133 patients, 36.1%; 95% CI, 33.4%–38.9%), whereas it remained uncertain whether these specific diagnoses were actually correct. Although complications such as pneumothorax and air leakage have been observed, no mortalities associated with these complications were reported. As a result, it would appear that transbronchial biopsy would not lead to a diagnosis in more than half of the patients (64%). It was advocated consequently that patients with probable, indeterminate, or alternative diagnosis patterns on HRCT are significantly more likely to have a detectable etiology within a transbronchial biopsy (e.g., sarcoidosis) than patients with a UIP pattern on HRCT. The ATS/ERS/JRS/ALAT guidelines, therefore, state that a diagnosis of IPF can be made without the need for a transbronchial/surgical biopsy after ruling out other causes of the UIP pattern with clinical presentation and anamnesis if a radiological definitive UIP pattern exists and also considering the fact that it does not merit taking the risk of complications (strong recommendation).[5] The authors are yet to reach consensus on whether or not a transbronchial biopsy should be routinely performed in patients with possible UIP, indeterminate UIP, or alternative diagnosis patterns on HRCT and therefore made no clear suggestion about the performance of a transbronchial biopsy as an alternative to surgical biopsy. It was emphasized that a transbronchial biopsy should be considered on a case-by-case basis.[5] The international guidelines other than the ATS/ERS/JRS/ALAT 2018 guidelines encourage the use of transbronchial biopsy in patients with IPF as a weak recommendation due to the low quality of evidence.[4,6,8]

Cryobiopsy has provided a good diagnostic yield in initial studies and is a safer option when compared to surgical lung biopsy.[27] Cryobiopsy has proven to have a greater diagnostic yield in the multidisciplinary diagnosis of IPF,[28] although its diagnostic accuracy has not been evaluated in a direct comparison with lung biopsy.[29] A review of studies involving cryobiopsies shows that lung cryobiopsy yields an adequate amount of sample in 96% of patients and eliminates the need for surgical biopsy by reaching a definitive diagnosis in approximately 80% of patients. When compared to surgical biopsy, lung cryobiopsy is associated with fewer respiratory tract infections and a lower risk of procedure-related mortality. Considering the fact that approximately 20% of patients cannot be diagnosed by lung cryobiopsy, and that patients exposed to cryobiopsy suffer hemorrhage and prolonged air leakage, the guidelines strongly recommend avoiding cryobiopsy in patients with a definitive UIP pattern on HRCT, given the risk of complications. That said, cryobiopsy can be considered as an alternative approach in experienced centers if radiological "possible" or "indeterminate" UIP or "alternative diagnosis" patterns exist on HRCT, and if the procedure is not contraindicated. The guidelines also advise making an effort to optimize the balance between diagnostic yield and complications and suggest that practices that have yet to start performing cryobiopsies should wait until the procedure has been standardized before introducing the method. Surgical biopsy (video-assisted thoracic surgery [VATS]) is the more common approach; however, not all centers are capable of and experienced in performing cryobiopsy. The Swiss guidelines do not include cryobiopsy, as the method is not performed routinely in their centers,[8] and the same guidelines recommend VATS over transbronchial biopsy in patients with possible IPF. The 2011 and 2018 ATS/ERS/JRS/ALAT guidelines use the same characteristics in terms of the histopathological findings and patterns detected after biopsy [Table 4]. Accordingly, international guidelines recommend that diagnosis be established through an evaluation of histopathological findings in patients undergoing surgical biopsy together with HRCT findings, after ruling out the known causes of ILD such as collagen tissue disease, asbestosis, and chronic hypersensitivity pneumonia[5,8] [Table 5]. Aside from this, international guidelines have also stated that a decision based on a multidisciplinary approach involving at least one chest disease specialist, a radiologist, and a pathologist experienced in ILDs is the optimum approach to the diagnosis of IPF.[4,6,8] Different from the 2011 guidelines,

Table 4: Histopathological criteria for the usual interstitial pneumonia pattern

UIP pattern (all of four criteria)	Probable UIP	Possible UIP pattern	Not UIP pattern
Marked fibrosis/structural distortion±predominant subpleural/paraseptal distribution of honeycombing	Some histologic features from column 1 are present, but to an extent that precludes a definite diagnosis of UIP/IPF and absence of features to suggest an alternative diagnosis or honeycombing only	Fibrosis with or without structural distortion, with features favoring either a pattern other than UIP or features favoring UIP secondary to another cause	Features of other histologic patterns of IIP in all biopsies (e.g., absence of fibroblast foci or loose fibrosis)
Patchy parenchymal fibrosis Presence of fibroblast foci Inconsistent with the diagnosis of UIP, presence of features suggestive of another diagnosis		Some histologic features from column 1, but with other features suggesting an alternative diagnosis	Histologic findings indicative of other diseases (e.g., hypersensitivity pneumonitis, Langerhans cell histiocytosis, sarcoidosis, and LAM)

IIP: Idiopathic interstitial pneumonias, UIP: Usual interstitial pneumonia, IPF: Idiopathic pulmonary fibrosis

the 2018 ATS/ERS/JRS/ALAT guidelines emphasize also that along with the decision on the final diagnosis, the determination of radiological patterns detected on HRCT, gathering a multidisciplinary council to make a decision on whether or not to perform BAL for diagnostic purposes and to determine the site of the lung biopsy, will contribute to the diagnosis.[5] Similar to the ATS/ERS 2018 guidelines, the Swiss guidelines highlight that the site of lung biopsy should be selected by a multidisciplinary council involving a chest disease specialist, a radiologist, and a thoracic surgeon.[8] It has been stated that specimens should be obtained from at least two lobes whenever possible, and that sampling from the ends of the middle lobe and lingula and from the sites of honeycombing must be avoided.

As a result, the ATS/ERS/JRS/ALAT 2018 guidelines strongly recommended against both transbronchial biopsy or cryobiopsy and surgical lung biopsy in patients with newly detected ILD with suspected IPF (after excluding other possible causes) who exhibit the UIP pattern on HRCT. The international guidelines state that a decision based on a multidisciplinary approach involving at least a chest disease specialist, a radiologist, and a pathologist experienced in ILDs can be considered the optimum method in the diagnosis of IPF[4,6,8] [Table 5].

A comparison of the ATS/ERS/JRS/ALAT guidelines for 2011 and 2018 is given in Table 3, whereas Table 6 makes a comparison of the diagnostic steps in all international guidelines.

Treatment

The approach to the treatment of IPF has changed substantially in recent years, with most of the previously used therapies having been abandoned due to lack of efficacy. More specifically, immunosuppressive therapies, for example, a triple therapy of prednisone, azathioprine, and NAC, have shown no benefits and have even been considered harmful.[30] The international guidelines also recommend against the use of corticosteroids, azathioprine, and acetylcysteine in the treatment of IPF.[8,31,32] The German guidelines do not recommend NAC monotherapy, whereas the Japanese guidelines state that most patients with IPF should not be treated with inhaled NAC, although this therapy might be a reasonable option in a small number of patients.[31,33] The guidelines also recommend against the use of Vitamin K antagonists, endothelin receptor antagonists, and phosphodiesterase 5 inhibitors in the treatment of IPF[31-33] [Table 7]. Table 7 presents a comparison of the therapies recommended in the international guidelines.

Table 5: Diagnosis of idiopathic pulmonary fibrosis based on high-resolution computed tomography and biopsy patterns

Suspected IPF*	Histopathological pattern			
	UIP	Probable UIP	Indeterminate UIP	Alternate diagnosis
HRCT pattern				
UIP	IPF	IPF	IPF	Not IPF
Probable UIP	IPF	IPF	IPF (probable)**	Not IPF
Indeterminate UIP	IPF	IPF (probable)**	Inconsistent with IPF***	Not IPF
Alternate diagnosis	IPF (probable)**/not IPF	Not IPF	Not IPF	Not IPF

*Patients clinically suspected of having IPF: Unexplained symptomatic or asymptomatic bilateral patterns of pulmonary fibrosis on a chest radiograph or chest computed tomography, particularly in patients older than 60 years, bibasilar velcro-type rales, **A diagnosis of IPF is probable if any of the following features exits: Moderate-to-severe traction bronchiectasis/bronchiolectasis in a male patient older than 50 years or a female patients older than 60 years, extensive (30%) reticulation on HRCT and an age ≥70 years, Increased neutrophils and/or absence of lymphocytosis in BAL fluid, Multidisciplinary discussion reaches a diagnosis of IPF, ***Indeterminate: Without an adequate biopsy is unlikely to be IPF, With an adequate biopsy may be reclassified to a more specific diagnosis after multidisciplinary discussion and/or additional consultation. HRCT: High-resolution computed tomography, IPF: Idiopathic pulmonary fibrosis, UIP: Usual interstitial pneumonia, BAL: Bronchoalveolar lavage

Table 6: Comparison of the guidelines in the diagnosis of idiopathic pulmonary fibrosis

	ATS 2011 Grade	ATS 2015 Grade	French 2013 Recommendation	German 2017 Grade	Swiss 2017 Recommendation	ATS 2018
BAL analysis	2	3	+	3	4	3
Transbronchial biopsy	2	3	NA	2	2	3
Serology	3	3	+	3	4	3
MDA	4	4	+	4	4	4
Genetic	-	-	+	2	2	2
Biopsy site	NA	Determined with MDY	NA	Determined with MDA	Determined with MDY	Determined with MDY
Pulmonary function test	NA	NA	FVC, DLCO, blood gases, 6-MWT	NA	3	3

4: Strong recommendation, 3: Weak recommendation, 2: Weak opposite recommendation, 1: Strong opposite recommendation, +: Recommendations for neither weak nor strong, -: Recommendations against neither weak not strong; NA: Not available, MDA: Multidisciplinary approach, FVC: Forced vital capacity, DLCO: Diffusion capacity, MWT: Minute Walking Test

Table 7: Comparison of treatment guidelines for idiopathic pulmonary fibrosis

Treatment	ATS 2011	ATS 2015	France 2013	Germany 2017	Switzerland 2017	Japan 2017
Acetylcysteine monotherapy	2	2	+	3	1	+
Ambrisentan	NA	1	-	NA	NA	NA
Anticoagulation	2			1		NA
Azathioprine, NAC, prednisone	2	1	-	1	1	NA
Bosentan	1	2	-	1		NA
Colchicine	1	NA	-	1		NA
Corticosteroid monotherapy	1	NA	-	1	1	1
Etanercept	1	NA	-	1		NA
Imatinib	No recommendation	NA	NA	1		NA
Lung transplantation	4	No recommendation for uni- or bilateral transplantation	+	4	4	NA
Invasive mechanical ventilation	2	NA	-	2	2	NA
Oxygen therapy	4	NA	+	4	4	NA
Nintedanib	NA	3	+	3	3	4
Pirfenidone	No recommendation	3	+	3	3	4
Pulmonary rehabilitation	3	NA	+	3	4	NA
Sildenafil	No recommendation	2	NA	NA		NA
Smoking cessation	NA	NA	NA	3		NA
Therapy for asymptomatic reflux	3	3	+	3	2	NA
PHT treatment	2	No recommendation	Only if severe	NA	1	NA
Influenza and pneumococcal vaccines	NA	NA	+	NA	NA	NA

4: Strong recommendation; 3: Weak recommendation, 2: Weak opposite recommendation, 1: Strong opposite recommendation, +: Recommendations for neither weak nor strong, -: Recommendations against neither weak not strong, NA: Not available, NAC: N-acetylcysteine, PHT: Pulmonary hypertension

No drug has been discovered to date for the treatment of IPF, although two antifibrotic drugs (disease-modifying drugs) have been identified that appear to slow disease progression: nintedanib and pirfenidone,[32,34] and of these, pirfenidone may have survival benefits. Patients with a confirmed interdisciplinary diagnosis of IPF, and those with mild-to-moderate disease based on pulmonary function tests, and who have no underlying liver disease and have an access to pirfenidone or nintedanib, are recommended to begin therapy with one of these drugs under the guidance of experienced physicians who are able to continue disease monitorization.

As an antifibrotic drug, pirfenidone inhibits the synthesis of collagen that is stimulated by the transforming growth factor beta; it reduces the extracellular matrix and blocks *in vitro* fibroblast proliferation. The ASCEND study, which was conducted to confirm the efficacy and safety of pirfenidone in IPF, randomized a total of 555 patients into two groups who would either receive oral pirfenidone for 52 weeks (2403 mg daily) or a placebo.[35] Pirfenidone provided a significant decrease in the yearly rate of FVC decline. In a pooled analysis of the data garnered in ASCEND, and the CAPACITY 004 and 006 studies, the likelihood of a 10% decline in FVC or reaching the threshold of death was >40% lower, and the likelihood of disease progression was 48% lower in patients receiving pirfenidone therapy for 1 year than in patients in the placebo group.[36]

In the extended ASCEND and CAPACITY studies, 34 patients from the pirfenidone arm and 68 patients from the placebo arm who showed a ≥10% decline in FVC in the first 3 or 6 months were reevaluated after 6 months.[37] The number of patients witnessing a ≥10% decline in FVC or death in the following 6 months was lower in the pirfenidone group than in the placebo group (2/34 and 19/68, $P < 0.009$). Despite the small sample size and the evidence of disease progression in the initial data, this study shows that the continuation of pirfenidone therapy may be beneficial for the patients. In a pooled analysis of the data from three randomized phase-3 studies that evaluated pirfenidone versus placebo (CAPACITY 004 and 006; ASCEND) and also from a meta-analysis of two studies in Japan, decreases were observed in all-cause mortality throughout the treatment, in mortality associated with IPF, and in mortality associated with IPF throughout the treatment period in favor of the pirfenidone group.[38]

Pirfenidone is administered orally at up to 40 mg/kg/day in three divided doses, with a maximum daily dose

of 2403 mg. The drug is initiated in doses of 267 mg (1 capsule) three times daily. At the end of 1 week, the dose is incremented to 534 mg (2 capsules) three times daily. As from the 2nd week of therapy, the drug is titrated to the full dose of 801 mg (3 capsules) three times daily. Pirfenidone must always be taken with food.

Liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and bilirubin) must be made before starting the therapy and repeated monthly for the first 6 months and every 3 months thereafter.[39] The most common side effects are rash (30%), photosensitivity (9%), nausea (36%), diarrhea (26%), abdominal discomfort (24%), dyspepsia (19%), anorexia (13%), and fatigue (26%).[39,40] The dose in patients receiving 2403 mg daily was reduced or interrupted in 18% of patients due to gastrointestinal side effects, and discontinued in 2%, although the administration of the drug between meals may alleviate gastrointestinal side effects.[41] Other potential side effects include diarrhea, constipation, pruritus, dry skin, hyperpigmentation, headache, and fatigue. A three times or higher increase than the upper limit of normal was observed in liver function tests in 4% of patients. Abnormal liver function tests returned to normal in all patients upon the dose reduction or discontinuation of therapy. An increase in ALT and/or AST may necessitate dose reduction or discontinuation. The dose of pirfenidone must be reduced if strongly or moderately potent CYP1A2 inhibitors (i.e., fluvoxamine and ciprofloxacin) are used.[42]

Pirfenidone has been recommended in both German[31] and international[8,32,33] guidelines for use in patients with IPF (weak recommendation, moderate level of evidence). The French guidelines recommend the use of pirfenidone in mild-to-moderate IPF.[7]

Nintedanib is a blocker of multiple tyrosine kinase receptors, mediating the production of fibrogenic growth factors (i.e., platelet-derived growth factor, vascular endothelial growth factor, and fibroblast growth factor) and reducing the progression rate of IPF.[43,44] Clinical trials have demonstrated that the main benefit of nintedanib is its reduction of the decline of pulmonary functions.[45-47] One study showed a prolonged time to the first exacerbation. A phase-2 study (TOMORROW) with nintedanib (BIBF 1120) provided promising results.[45] A total of 432 patients were randomly assigned to four oral doses of BIBF 1120 and to a placebo. The group of patients who received the highest dose of BIBF 1120 (150 mg twice daily) showed a slower decline in pulmonary functions and a trend toward the experiencing of a lower number of exacerbations than the placebo group.

In two phase-3 studies that followed this initial study (INPULSIS-1 and INPULSIS-2), a total of 1066 patients were randomized to receive either nintedanib 150 mg twice daily for 52 weeks or a placebo.[43]

In the INPULSIS-1 study, the yearly decline in FVC was lower in the nintedanib group (125.3 mL) than in the placebo group (95% CI: 77.7–172.8), and the INPULSIS-2 study yielded similar results, with a decline in FVC of 93.7 mL/year (95% CI: 44.8–142.7). In the INPULSIS-1 study, no difference was observed between the nintedanib group and the placebo group in terms of the mean time to first exacerbation. However, the INPULSIS-2 study observed an increase in the meantime to first exacerbation (hazard ratio [HR]: 0.38, 95% CI: 0.19–0.77). In a subgroup analysis of these studies, the treatment effect was found to be more remarkable in patients with a baseline FVC of ≤70% than predicted.[46]

Nintedanib is administered 150 mg twice daily at approximately 12-h intervals through the oral route. Nintedanib should not be administered to patients with moderate-to-severe liver damage (Child–Pugh B or C).[48] Liver function tests must be obtained monthly in the first 3 months after initiating the therapy, and every 3 months thereafter, considering clinical indications. An elevation in liver enzymes may necessitate dose reduction or discontinuation. Women of childbearing age should undergo pregnancy testing before initiating therapy, and pregnancy must be avoided until at least 3 months after the last dose is received.[48] Nintedanib interacts with P-glycoprotein and CYP3A4 inhibitors and inductors and also increases the risk of bleeding in patients receiving full-dose anticoagulant therapy.

The most common side effects associated with the use of nintedanib are diarrhea (62%), nausea (24%), vomiting (12%), and an elevation in liver function tests to five times the upper normal limit, as observed in 6% (14%) of patients.[45,48] In clinical trials, diarrhea necessitated dose reduction in 11% and drug discontinuation in 5% of patients, and it required hydration and the use of antidiarrhea medications (e.g., loperamide) and sometimes the reduction of the drug dose to 100 mg twice daily. The drug must be discontinued if the reduced dose cannot be tolerated.

Similar to pirfenidone, nintedanib is now recommended in international guidelines,[31-33,49] although neither of these drugs can be regarded as superior to the other due to the lack of a direct comparison. The magnitude of the effect on FVC decline seems to be comparable between the two drugs. At present, the decision of which of the two drugs is to be prescribed should be based essentially on the side effect profile and contraindications to treatment and comorbidities.

Although clinical trials on pirfenidone and nintedanib have included patients with mild-to-moderate IPF, the

Food and Drug Administration has approved both drugs for all patients with IPF, without restriction. The initiation of therapy upon the establishment of a diagnosis seems to be reasonable in improving the patients' prognosis and reducing disease progression. The available data in literature regarding antifibrotic therapy with either pirfenidone or nintedanib show comparable efficacy in reducing disease progression in all studied degrees of functional severity. It is worthy of note that patients with a "normal" FVC (>90% in the nintedanib group and ≥80% in the pirfenidone group) in the placebo arms witnessed a more significant reduction in absolute FVC than patients with significant restriction. It would seem that baseline FVC in the nintedanib group does not influence treatment effects, and for this reason, a spirometry showing values within the normal predicted ranges should not be considered a reason for withholding antifibrotic therapy in patients with IPF.[39,46,47,50,51]

The international guidelines also recommend the initiation of antifibrotic therapy at the time of initial diagnosis in symptomatic patients with a definitive diagnosis of IPF (preferably diagnosed following a multidisciplinary discussion).[32,33,49] However, the German and Swedish guidelines state that watchful waiting until initiating the therapy may be justified in selected cases (e.g., incidental finding on CT scans or lung resection) with no or minimal restriction on pulmonary functions, as well as in asymptomatic patients.[8,31] It has also been emphasized that the presence of an accompanying disease that restricts prognosis (e.g., lung cancer) may be a reason for withholding antifibrotic therapy, and that the individualized therapeutic approach in all cases must be openly and intelligibly discussed with the patient. In the event of no therapy being initiated, it is stressed that patients must be followed every 3–6 months and reevaluated for the initiation of therapy.[8,31]

Although patients with possible IPF were included in the INPULSIS study[47] with nintedanib therapy, and a predetermined subgroup analysis (gender, age, race, baseline FVC, systemic corticosteroid use, etc.) showed more consistent effects of nintedanib therapy on possible UIP than on definitive UIP, the guidelines recommend that a decision to start antifibrotic therapy should be made in a multidisciplinary environment for patients with possible or probable UIP. Lung fibrosis other than IPF may come with overlapping disease mechanisms, although disease course and prognosis are considerably varied in patients with lung fibrosis other than IPF. Unlike IPF, fibrotic ILD occurring in patients with connective tissue disease may benefit from immunosuppressive therapy.

The effect of pirfenidone or nintedanib on ILD associated with connective tissue disease is unknown, although studies are continuing.[52]

Regarding the duration of therapy, guidelines suggest that a well-tolerated antifibrotic therapy must be continued without restriction, or possibly with a switch between two approved antifibrotic drugs until lung transplantation, considering the high mortality associated with IPF. It has also been reported that a discontinuation of antifibrotic therapy or dose reduction may be required if significant drug-related side effects occur, and that it is safe to switch from one drug to another.

Pirfenidone has been well tolerated over a 10-year treatment period.[41,53] Considering the fact that the pathophysiological mechanisms of IPF develop and decelerate over months or years, a specific therapy should often not be discontinued in the event of the disease course not ceasing or being reversed by either nintedanib or pirfenidone. A recent study showed that the continuation of therapy in patients with progressive IPF, despite the use of pirfenidone therapy, is associated with better outcomes when compared to those receiving a placebo.[37]

It has been well documented in larger cohorts that a >10% decline in FVC within 6 months is associated with an increased risk of death.[54,55] In a preliminary analysis of the CAPACITY and ASCEND studies, patients exhibiting a >10% FVC decline within 6 months showed better disease course and prognosis under pirfenidone therapy when compared to the placebo group.[56] Similar data published discretely to date are also available for nintedanib.[57] Switching to nintedanib therapy may be possible in the event of drug intolerance or following disease progression while undergoing pirfenidone therapy.[58]

In terms of combining the two drugs, a Japanese stage 2 study investigated the side effects, tolerability, and pharmacokinetics for nintedanib alone and combination profile for pirfenidone alone in patients with IPF. The research revealed that combination therapy with pirfenidone reduced maximum plasma levels and was associated with more frequent side effects when compared to nintedanib monotherapy.[58] Accordingly, the international guidelines recommend avoiding combination therapy with nintedanib and pirfenidone in patients with IPF due to the lack of evidence of the benefits of such an approach.

Aside from the use of antifibrotic drugs, the management of IPF also includes smoking cessation, vaccination, pulmonary rehabilitation (PR), transplantation, and the treatment of attacks and comorbidities.

Treatment Approach to Idiopathic Pulmonary Fibrosis and Comorbidities

Gastroesophageal reflux

The prevalence of gastroesophageal reflux (GER) in patients with IPF is estimated to be 66%–87%. It has been noted that patients may be asymptomatic, although acid reflux has been demonstrated in 33%–53% of patients. GER is a risk factor for aspiration and microaspiration that causes IPF and may lead to pneumonia.[59] The regular use of anti-acid therapies such as proton-pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs) may reduce the lung damage associated with microaspiration.[60,61]

Observational studies have sought the role of regular PPI and H2RA use in reducing disease progression in patients with IPF.[60,62-64] A retrospective analysis of a cohort study revealed the survival benefit in patients receiving anti-acid therapy.[62,63] In another study, all patients with IPF were evaluated after being randomized into pharmacological therapy and placebo groups.[62] The 124 patients receiving PPI or H2 blockers at the outset were compared with 118 patients undergoing no anti-acid therapy, and in this analysis, a significantly smaller decrease in FVC was observed in those who received anti-acid therapy at the outset. Although the patients receiving anti-acid therapy suffered no acute exacerbations (AEs) when compared to those receiving the placebo, there was no difference in all-cause mortality and the reasons for hospitalization. That said, a meta-analysis of observational studies revealed that PPIs do not increase the risk of hospitalization due to community-acquired pneumonia in the general population,[65] and the potential drug interactions between PPIs and other IPF medications, and the effects of therapy in patients with IPF in the long term, are still unknown. Based on these results, the ATS/ERS/JRS/ALAT 2015 guidelines conditionally recommended anti-acid therapy in patients with IPF. There is consensus regarding the use of a therapy if GER symptoms exist and on the withholding of therapy if the patient is asymptomatic.[32]

Similar to the ATS/ERS/JRS/ALAT 2015 guidelines, the Swiss guidelines also recommended anti-acid therapy in symptomatic patients with IPF and recommended against anti-acid therapy in asymptomatic patients due to a lack of evidence.[8] The effect of anti-acid therapy on the progression of disease has been evaluated against a placebo in a phase II trial of pirfenidone (CAPACITY and ASCEND). A total of 624 patients were included, 291 of whom received anti-acid therapy, and no significant difference was found in all-cause mortalities, although a decline in FVC of more than 10% was noted between the treated and untreated patients. At the same time, no significant increase in pulmonary infections was observed among the patients receiving anti-acid therapy.[66] The German and Japanese guidelines made no mention of GER,[31,33] while the Spanish guidelines stated that randomized, placebo-controlled studies are required to determine the benefits of anti-acid therapy in patients with IPF.[49]

Pulmonary Hypertension

Patients may also develop PH despite fibrosis being the main problem. PH in lung diseases falls into group II in the classification of PH. A diagnosis of PH requires a mean pulmonary artery pressure of 25 mmHg or higher and a pulmonary capillary wedge pressure of 15 mmHg or lower in a right heart catheterization.

PH must be suspected if the symptoms are more severe than suggested by pulmonary function tests in patients with IPF, if the functional impairment is disproportional to the clinical deterioration and if symptoms of right heart failure exist.

In the 2011 guidelines, the recommendation was against the use of drugs for PH treatment, as a very limited evidence was taken into consideration in IPF patients. The studies included within these guidelines did not randomize patients to the treatment and control groups and focused on short-term hemodynamic outcomes rather than the long-term outcomes.[67-70] Subsequent randomized and controlled studies evaluating the treatment of IPF patients with ambrisentan and sildenafil included a subgroup analysis patients with IPF and comorbid PH. The "Sildenafil Trial of Exercise Performance in Idiopathic Pulmonary Fibrosis" evaluated the efficacy of sildenafil, and the primary endpoint was 20% or greater improvement from baseline in a 6 MWT. However, no significant effect was observed when compared with placebo.[71] In another study involving a prespecified analysis of echocardiographic data (119 out of 180 patients), sildenafil was demonstrated to have preserved the 6-min walk distance in a subgroup of 22 patients with right ventricular systolic dysfunction when compared to the placebo.[72]

The study entitled "Placebo-Controlled Study to Evaluate Safety and Effectiveness of Ambrisentan in Idiopathic Pulmonary Fibrosis" evaluated the efficacy of ambrisentan. When ambrisentan was administered at a dose of 10 mg/day to patients aged 40–80 years with minimal fibrosis and without honeycombing who had FVC >69%, the number of hospital admissions and disease progression were higher in the treatment arm when compared to the placebo group, whereas no significant difference was found in mortality, and the study was terminated prematurely.[73] On the basis of these results, the ATS 2015 IPF guidelines reported that

the use of ambrisentan is contraindicated whether or not PH exists.[32] Riociguat therapy has been attempted in patients with idiopathic interstitial pneumonia and PH; however, the study was terminated prematurely due to concerns of increased mortality when compared to the placebo.[74]

Based on the results of these studies, the panelists of the 2015 guidelines stated that further evidence was required and made no recommendation regarding the treatment of PH in patients with IPF.[32]

The Spanish guidelines recommended that patients with PH or with severe right ventricular dysfunction should be considered for individualized therapy (weak recommendation, low level of evidence), and it was also stated that ongoing clinical studies combining pulmonary vasodilators with antifibrotic agents would show whether or not this approach is beneficial.[49] The Swiss guidelines make no recommendation of treatment for PH associated with IPF, although the guidelines highlighted that a patient suspected of having PH independent from IPF should undergo particular evaluation in a dedicated center experienced in PH and interstitial pulmonary diseases.[49] The German and Japanese guidelines made no mention of this issue.[31,33]

Idiopathic Pulmonary Fibrosis and Lung Cancer

Another comorbidity is the lung cancer that may accompany IPF. Epidemiological evidence suggests that 22% of patients with IPF develop lung cancer, with the risk being approximately five times higher than in the general population.[75] Despite the vast amount of epidemiological and mechanical evidence suggesting a connection between IPF and lung cancer, very little is known about the diagnosis and management of such patients.

Neither the most recent ATS/ERS/JRS/ALAT guidelines, which were updated in 2015, nor the Spanish, Swedish, or German guidelines have addressed this issue.[8,31,32,49]

The Japanese guidelines mentioned IPF and comorbid lung cancer in their review of several studies. The incidence of AE following surgery and overall survival from lung cancer with comorbid IPF may be affected by the differences in surgical procedures and the severity of IPF prior to surgery. They state, however, that no clear statement can be made due to the presence of a number of studies involving retrospective case series.[33] This guideline also evaluated multicenter studies involving a larger number of cases that yielded less uncertain data, with a 5-year survival rate of 40% being reported in surgical patients with nonsmall cell lung cancer and accompanying interstitial pneumonia.[76] The rate of AE following surgery was reported to be 9.3%, and the mortality rate was reported to be 43.9% among the patients diagnosed with nonsmall cell lung cancer, some of which were found to be interstitial pneumonia. In the same study, the incidence of AEs was found to be 10.3% in a subgroup analysis of 1300 patients for whom a UIP imaging pattern was available.[77,78] Based on the above-mentioned evidence, the Japanese guideline committee recommended surgery in eligible patients with lung cancer with comorbid IPF or other IPs. Nintedanib was initially approved for use in combination with docetaxel-based second-line therapy in the treatment of nonsmall cell lung cancer.[78] Retrospective data suggest that preoperative pirfenidone therapy would have a beneficial effect on the incidence of postoperative AEs in patients with adenocarcinoma and IPF.[79] The Japanese guidelines, therefore, recommended against the administration of protective drugs against AEs (excluding antifibrotic drugs) following surgery in patients with lung cancer and accompanying IPF or other IP.[33]

Both prospective and retrospective studies have been published on the administration of chemotherapy in patients with lung cancer and IPF. In a prospective study evaluating the safety and efficacy of first-line therapy with carboplatin and weekly paclitaxel in 18 patients with NSCLC and interstitial pneumonia (6 patients with IPF), Minegishi *et al*.[80] reported AEs in 1 (5.6%) out of 18 patients. In a retrospective study of 19 patients with NSCLC (including 16 patients with IPF) evaluating the efficacy of first-line therapy with carboplatin/cisplatin (CDDP) and vinorelbine, Okuda *et al*.[81] reported AEs in 3 (15.8%) patients.

In another study, AE was observed in two patients with NSCLC in the second series of patients with IPF that received pemetrexed therapy, whereas no mortality was observed.[82] In a prospective study by Minegishi *et al*. that evaluated 17 patients[83] with small-cell lung cancer and interstitial pneumonia (including 8 patients with IPF) who received first-line therapy with carboplatin and etoposide, AE was observed in 1 (5.9%) out of 17 patients. The rate of AEs was reported to be 15.4% in another study of 120 patients with SCLC and interstitial pneumonia (59 with IPF) who received chemotherapy.[84] Following all these studies, the panelists in the Japanese guidelines stated that patients with lung cancer with comorbid IPF or other interstitial pneumonias should receive chemotherapy, although this line of therapy may not be a reasonable option in a small number of patients. No recommendation was made regarding radiotherapy.[32]

Acute Exacerbation

AEs-IPF are defined as sudden clinical and functional impairments that occur during the course of IPF. The natural course of IPF can vary considerably, and it is difficult to predict a patient's clinical course. The disease shows rapid progression in some patients with functional impairments occurring in a short period, whereas other patients show a slower disease course. AEs of IPF cause a rapid deterioration in disease course and account for the majority of IPF-related mortalities. This clinical situation is responsible for a significant proportion of the mortalities seen in IPF, although the etiology has yet to be elucidated. No randomized controlled study has been conducted to date specifically addressing the treatment of AE-IPF. Although corticosteroids, antibiotics, and the modalities of supportive therapy are commonly used in the treatment of AE-IPF, there have been studies in literature evaluating the use of cyclophosphamide, tacrolimus, cyclosporine, polymyxin, and methods such as hemoperfusion and plasmapheresis.

Supportive therapy and corticosteroids are recommended for the treatment of AE-IPF in the ATS/ERS/JRS/ALAT 2011 guidelines, the latter presenting a low level of evidence. The updated 2015 guidelines made no update of their recommendations in this regard. The French guidelines for the treatment of AE-IPF recommend the use of intravenous cyclophosphamide therapy other than corticosteroids and supportive therapy, anticoagulation in cases with suspected thromboembolism, and broad-spectrum antibiotics when infections cannot be ruled out.[85]

There have to date been no randomized studies supporting the addition of a second immunosuppressive drug (i.e., azathioprine, cyclophosphamide, or cyclosporine), and also no controlled studies supporting the use of low-molecular-weight heparin in the treatment of exacerbations, unless the presence of concurrent venous thromboembolic disease is suspected. The empirical use of broad-spectrum antibiotics is considered appropriate in clinical practice due to the difficulties in ruling out an underlying opportunistic infection.[44,86-88] There have been no further research to date evaluating the efficacy of novel antifibrotic medications in the treatment of exacerbations of IPF, although data exist suggesting a preventive effect.[89] The spanish guİdeline, recommended the administration of influenza and pneumococal vaccines as the most important intervention for the prevention AEs. The avoidance of surgical bıopsy in patients with impairment in pulmonary functions of a typıcal pattern of ıntertitial pneumonia is noted on HRCT.[49]

The Swiss guidelines recommend that pirfenidone or nintedanib therapies be withheld during exacerbations in patients with IPF that require hospitalization, but suggest that antifibrotic agents may be continued if initiated beforehand.[8] As a practical approach, the administration of antibiotics is recommended in cases where an infection cannot be ruled out definitely. As the role of corticosteroids remains uncertain, it is recommended that a short course of steroid therapy (administration of methylprednisolone for a couple of days) be considered under certain circumstances.[8]

The Japanese guidelines recommend treatment with corticosteroids (including the use of pulse steroid therapy) in patients with AEs-IPF. They further extend their recommendations to the use of immunosuppressive agents during exacerbations, but stress that this therapy may not be a reasonable option in a small number of patients. They also recommend against the use of neutrophil elastase inhibitors and recombinant thrombomodulin during AEs, but emphasize that this therapy may be a reasonable option in a minority of patients.[33]

Combined Pulmonary Fibrosis and Emphysema Syndrome

Combined pulmonary fibrosis and emphysema (CPFE) is a recently described syndrome with unique clinical findings that is characterized by radiologically detected upper-lobe emphysema and lower-lobe fibrosis. The characteristic features of these patients are older men who smoke, and preserved lung volume and decrease diffusion capacity.

There is no specific treatment for this condition. Occasional improvement in hemodynamic parameters and rare clinical improvement has been reported following pulmonary arterial hypertension-specific therapy in patients with CPFE.[89,90] Cessation of smoking, oxygen therapy, infection control, and palliative care are recommended. The ATS/ERS/JRS/ALAT, German, Japanese, and Swedish guidelines have made no mention of this condition, whereas the Spanish guidelines recommend a palliative approach (smoking cessation, oxygen therapy, and infection control). Recent studies have reported pirfenidone to be well tolerated, and to ensure a stable disease course in most patients with IPF, including those with cardiovascular disease and emphysema, while there is no evidence of the specific efficacy of pirfenidone or nintedanib in CPFE.

Palliative Approach

Lung transplantation

Lung transplantation has become a life-saving treatment option, improving the quality of life in patients with end-stage diffuse parenchymal lung disease

and particularly in those with IPF. Considering the unpredictable and variable clinical course of IPF, patients must be referred for the evaluation of lung transplantation upon initial diagnosis, regardless of their pulmonary functions. A number of recently introduced novel therapies may postpone the need for lung transplantation in patients with mild-to-moderate IPF, although lung transplantation remains the definitive treatment for advanced-stage disease.

All studies in current literature discussing whether lung transplantations should be unilateral or bilateral are retrospective in nature, and most rely on analysis results without adjusting for confounding factors. There is still a lack of consensus on the most appropriate method, although the available retrospective studies favor bilateral transplantation in IPF.[91] In a pooled survival analysis of three observational studies, no significant difference was noted between patients undergoing unilateral and bilateral lung transplantations (HR, 0–47; 95% CI, 0.19–1.17).[92-94] When the data of another four studies were evaluated that were not included in the pooled analysis, given the lack of reported HRs, the patients who underwent bilateral lung transplantations did not differ significantly from those who underwent unilateral lung transplantation in terms of survival.[95-97]

Relating to these results, the ATS/ERS/ALAT/JRS 2015 guidelines stated no preference between bilateral or unilateral lung transplantations.[32]

The Swiss guidelines suggest that the possibility of lung transplantation should be considered at the time of initial diagnosis in all patients with IPF, even if lung functions are initially preserved, and also that patients with IPF aged younger than 65 years should be referred to a transplantation center in the early period for initial assessment before clinical or functional deterioration occurs, despite antifibrotic therapy, if no significant comorbidities or contraindications exist.[8] It is also emphasized that cooperation is required between the transplant center and the attending pulmonology unit after the patient has been placed on the lung transplant waiting list in order to keep the patient eligible for transplantation. Lung transplantation was not included in the Spanish, German, or Japanese guidelines.[31,33]

Pulmonary Rehabilitation and Oxygen Therapy

Progressive pulmonary restriction, ventilatory failure, and impaired gas exchange in IPF can cause an increase in dyspnea perception and a decrease in exercise capacity and functional capacity, along with impairment in the quality of life. Exercise training, as the most important component of PR, is a safe and effective approach in the prevention of chronic respiratory disease and in the management of complications. The Japanese and Swiss guidelines recommend PR in patients with IPF, whereas the ATS/ERS 2015 guidelines and the Spanish and German guidelines make no mention of PR.

Among the paucity of studies, one retrospective analysis indicated that oxygen support would be beneficial for exercise performance in patients with IPF.[98] Both the Swiss and Japanese guidelines recommend the administration of oxygen therapy in the chronic phase of IPF.

Acknowledgment

The authors would like to thank the Turkish Respiratory Society for their support in the translation of this manuscript.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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