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REVIEW ARTICLE

Update in diagnosis and treatment of idiopathic pulmonary fibrosis

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ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is a rare disease characterized by chronic, fibrosing, progressive, and irreversible lung involvement of unknown etiology and poor prognosis. It is considered a complex disease resulting from the interaction between genetic susceptibility, cellular and molecular aging, and repeated environmental exposures. This review is part of a position paper on the diagnosis and treatment of IPF, developed by the clinical-radiological-pathological study group on diffuse interstitial lung diseases of the Catalan Society of Pulmonology. Based on published clinical evidence, it highlights key aspects of the diagnostic process: a systematic approach that includes invasive procedures (such as lung biopsy) in selected cases, the central role of multidisciplinary discussion, and the importance of genetic testing. Moreover, holistic therapeutic management of IPF is essential, combining antifibrotic therapy with supportive and non-pharmacological interventions such as supplementary oxygen, pulmonary rehabilitation, symptom control strategies, patient education, and palliative care.

Keywords: Idiopathic pulmonary fibrosis. Early diagnosis. Multidisciplinary team. Antifibrotic agent.

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INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is the most common type of idiopathic interstitial pneumonia. It is a rare disease characterized by a chronic, fibrosing, progressive, and irreversible involvement limited to the lung, of unknown cause and poor prognosis, associated with a histopathological and/or radiological pattern of usual interstitial pneumonia (UIP)[1]. In recent years, an increase in prevalence has been observed, likely related to an aging population, greater sensitivity and visibility of the disease, an increase in the use of computed tomography (CT) of the chest, and the context of the COVID-19 pandemic[2].

The currently accepted pathophysiological theory is based on the aberrant activation of alveolar epithelial cells. These cells secrete growth factors and matrix metalloproteinases, which promote the proliferation of fibroblasts and myofibroblasts, disruption of the basement membrane, and excessive production of extracellular matrix, leading to the progressive destruction of lung architecture. Simultaneously, these fibroblasts and myofibroblasts produce mediators and enzymes that further damage the epithelium and basement membrane, perpetuating the process of chaotic lung remodeling and resulting in irreversible pulmonary fibrogenesis[3]. Patients with IPF exhibit most of the hallmark features of aging, such as telomere dysfunction with abnormal telomere shortening, genomic instability, epigenetic changes, mitochondrial dysfunction, increased oxidative stress, and cellular senescence[3,4]. These processes cause a loss of alveolar epithelial integrity in genetically predisposed individuals, resulting in a deterioration of the proper reparative capacity in response to repeated external insults (viruses, pollution, microaspirations, and tobacco smoke)[3,5]. Several potential risk factors for IPF have been described, including smoking, occupational and environmental exposures, viral infections, gastroesophageal reflux, and genetic factors[1,3].

CLINICAL, RADIOLOGICAL, AND HISTOPATHOLOGICAL CHARACTERISTICS OF IPF

The typical presentation of IPF is a patient aged 65-70, with progressive dyspnea and dry cough, bibasilar crackles, and, often, finger clubbing. These symptoms cause limitations in exercise capacity and activities of daily living, resulting in a significant decrease in quality of life (QoL). Patients experience a progressive decline in lung function leading to respiratory failure. The course of the disease is variable and, at the time of diagnosis, difficult to predict. Some patients progress rapidly, whereas others have a slower progression. Overall survival is generally estimated to be between 2 and 5 years from symptom onset[1].

The UIP pattern is the characteristic radiological pattern of IPF, but it is not specific to the disease. It can also be observed in other fibrosing interstitial lung diseases (ILDs), especially asbestosis, fibrotic hypersensitivity pneumonitis (HP), and systemic autoimmune diseases (SADs)[6,7]. The most common features of the UIP pattern in high-resolution CT (HRCT) are the symmetrical presence of areas of fine reticulation with intralobular linear opacities, thickening of interlobular septa,

architectural distortion, and traction bronchiectasis/bronchiolectasis, ground-glass opacities (GGO), and honeycombing (especially in subpleural areas and in the pulmonary bases). In most patients, the presence of GGO is lower than reticulation[6,7]. Occasionally, patients may have a probable UIP pattern or an indeterminate pattern. The probable UIP pattern is characterized by the presence of reticulation, traction bronchiectasis/bronchiolectasis, but with the absence of honeycombing; the indeterminate pattern refers to a fibrosing ILD in which the findings and distribution are neither UIP nor probable UIP nor suggest any alternative diagnosis[6].

The definition of the histopathological UIP pattern includes the presence of patchy interstitial fibrosis, fibroblast foci, and architectural distortion[8]. Although the UIP pattern is characteristic of IPF, several important points should be highlighted. It may also be observed in other diseases, such as connective tissue diseases, HP, asbestosis, and familial pulmonary fibrosis[1,9,10]. Moreover, certain histopathological findings may suggest that the UIP pattern has a secondary cause and, therefore, does not correspond to IPF: inflammation in non-fibrotic areas, frequent lymphoid follicles with germinal centers, and peribronchiolar inflammation with multinucleated giant cells or granulomas[5,11].

DIAGNOSIS OF IPF

Clinical suspicion and diagnostic delay

Clinical suspicion of IPF is established in an individual over 50 years old presenting with persistent cough and dyspnea on exertion, "velcro-type" crackles on lung auscultation, with or without digital clubbing[12]. The presence of crackles is such a sensitive clinical sign that it has recently been proposed to aid in the early detection of fibrosing ILD. Early referral to multidisciplinary units with specialists dedicated to ILDs should be considered for these patients with suspected IPF.

It should be noted that the diagnostic delay for IPF ranges from 1 to 2 years; this delay is multifactorial and is associated with increased mortality[13]. Therefore, early diagnosis and treatment in IPF patients can improve the prognosis of the disease. Figure 1 details the main factors related to diagnostic delay and potential improvement strategies[13].

Diagnostic assessment

Figure 2 illustrates the diagnostic assessment in IPF patients.

Medical history

A targeted interview to search for a possible cause of ILD is a strong recommendation in the IPF management guidelines[6]. The medical history should be systematic and comprehensive, including the following aspects: smoking status, medication use, family history of ILDs, environmental exposures at work, at home, and frequently visited places, and comorbidities. In addition, the presence of symptoms and signs of SAD should be evaluated.

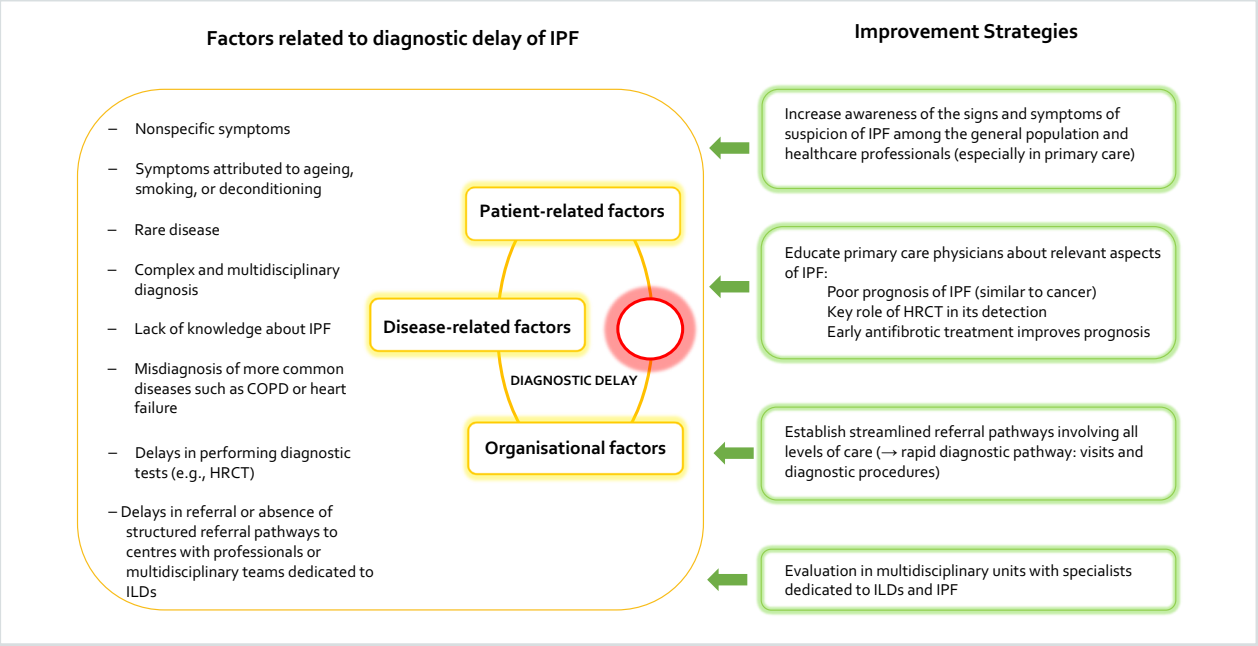

Figure 1. Main factors related to diagnostic delay and potential improvement strategies. ILD: interstitial lung disease; HRCT: high-resolution computed tomography; IFP: idiopathic pulmonary fibrosis; COPD: chronic obstructive pulmonary disease.

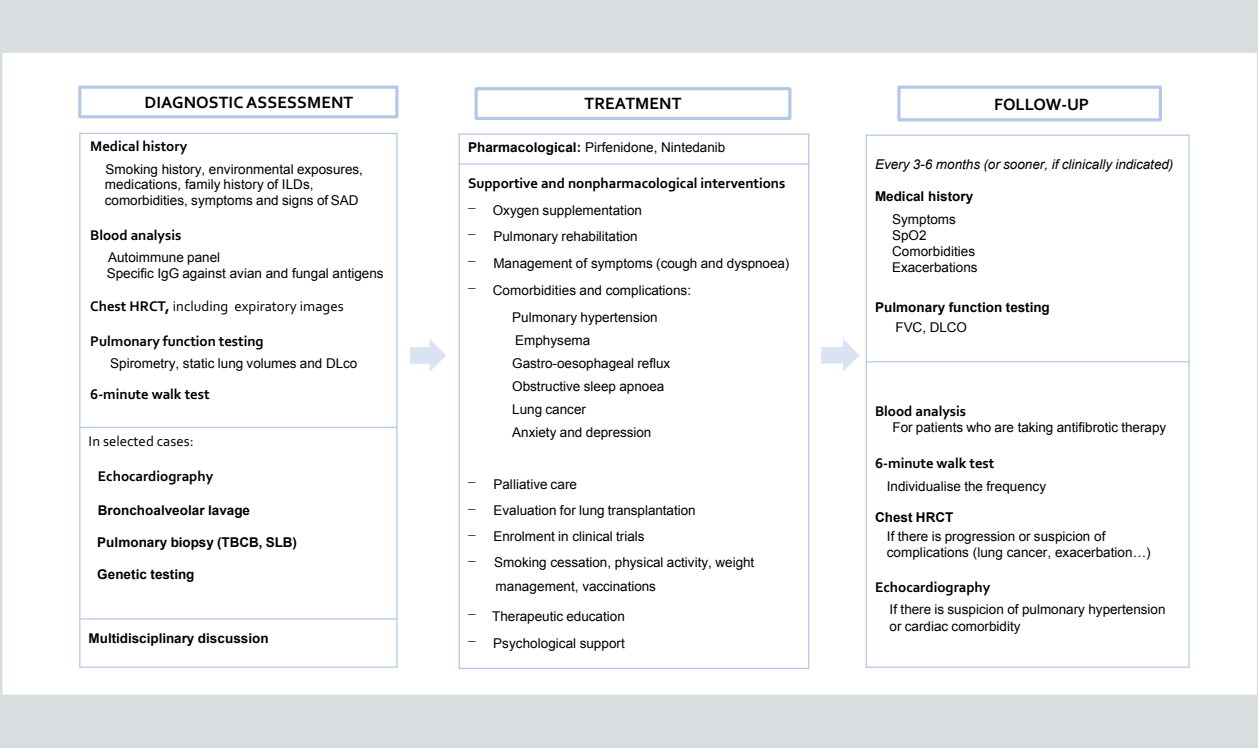

Figure 2. Diagnostic assessment in idiopathic pulmonary fibrosis patients (*adapted from reference 6*). SAD: systemic autoimmune disease; ILD: interstitial lung disease; IgG: immunoglobulin G; HRCT; high-resolution computed tomography; DLCO; diffusing capacity for carbon monoxide; TBCB: trasbronchial cryobiospy; SLB: surgical lung biopsy; Sp02: saturation of peripheral oxygen; FVC: forced vital capacity.

Blood analysis

Blood analysis plays an important role in the diagnostic process of IPF to rule out possible causes of ILD, especially HP and SADs. The 2018 clinical practice guidelines from the American Thoracic Society/European Respiratory Society (ERS) recommend performing autoimmune markers to aid in ruling out SADs. Most panelists recommend a general study that includes antinuclear antibodies, rheumatoid factor, anti-citrullinated peptide antibodies (anti-CCP), and a myositis panel. Based on initial clinical and analytical findings, a more targeted study may be considered, although a minority recommend comprehensive testing from the outset[6]. In clinical practice, the autoimmune antibody panel may vary between centers; nonetheless, most institutions perform an initial comprehensive autoimmune assessment.

In addition, it is recommended to determine specific immunoglobulin G antibodies against avian and fungal antigens, as these are the most common etiological agents even in the absence of a reported history of significant exposure[14]. Other prognostic markers, such as MMP-7, SPD, CCL-18, or KL-6, are not yet recommended as routine tests due to the lack of clinical validation.

Imaging thoracic techniques

Chest HRCT is the imaging technique of choice when IPF is suspected. HRCT is more sensitive than conventional CT and simple chest X-ray in the detection and characterization of ILDs and small airway disorders. The term HRCT combines the use of the finest collimation (< 2 mm thickness) with reconstruction algorithms designed to achieve high spatial resolution. A thin slice thickness decreases the partial volume and improves the ability of CT to demonstrate small lung lesions. This thickness is roughly equivalent to the size of the anatomical structures of interest of the secondary lung lobe. Expiratory images should be performed routinely at the initial examination. In addition, images in the prone position are optional in case of suspicion of early ILD or to resolve issues (densities in dependent areas in the supine position)[15].

Bronchoalveolar lavage (BAL)

BAL is traditionally used in the evaluation of ILDs. By analyzing the cellular composition of the fluid obtained, BAL can reveal findings characteristic of specific ILDs. Proper standardization of the technique, in accordance with current guidelines, and expert cytopathological interpretation are essential for accurate result assessment[16]. BAL is a technically simple procedure that is generally well tolerated, even in patients with acute conditions in critical care settings. BAL is currently considered a diagnostic option in patients with suspected IPF who present with an indeterminate pattern on HRCT in international clinical guidelines[6]. In contrast, in patients with a definite or probable UIP pattern on HRCT, the use of BAL is generally discouraged unless clinically indicated on a case-by-case basis.

Transbronchial cryobiopsy (TBCB) and surgical lung biopsy (SLB)

In patients with clinical suspicion of IPF and a chest HRCT showing a UIP or probable UIP

pattern, additional invasive procedures are not required. However, in cases with an indeterminate or non-UIP pattern, or in those without clinical suspicion where non-invasive studies (including serology) do not provide a conclusive diagnosis, lung biopsy may be necessary. Historically, SLB has been considered the procedure with the highest diagnostic yield. Currently, SLB is recommended to be performed via video-assisted thoracoscopic surgery. Conventional transbronchial biopsy (TBB) is not recommended for IPF diagnosis due to its limited utility in identifying the UIP pattern. More recently, TBCB has been introduced, implementing the use of cryoprobes. The samples obtained are larger and have fewer artefacts compared to conventional TBB, which allows expanding the diagnostic range, including the UIP pattern. Assessing risks/benefits, this technique has been included in the diagnostic algorithm of IPF in the latest update of the international guidelines[6] as an alternative to SLB in those centers with sufficient experience in this technique. Importantly, adequate experience is required not only in obtaining the tissue samples but also in their histopathological interpretation before implementing the technique in clinical practice. Therefore, in clinical practice, the key question is determining which procedure is most appropriate for each case. For this reason, the clinical-radiological-pathological study group of ILDs (CRAMPID) of the Catalan Society of Pulmonology developed a proposal that was published in 2020[17].

The main complications of TBCB are bleeding (up to 30% of cases) and pneumothorax (around 9%), which may sometimes be severe. The estimated procedure-related mortality is approximately 0.7%. In comparison, SLB has an estimated mortality of about 1.8% and higher morbidity, including post-operative pain and the risk of disease exacerbation. Therefore, although the diagnostic yield of TBCB is slightly lower, it is regarded as a safer procedure.

It is also important to highlight that various studies have shown that incorporating TBCB findings into the multidisciplinary discussion (MDD) can help reach a diagnosis in 70-80% of cases. Based on all this, although these data refer to the diagnosis of ILD and not specifically of IPF, given its better safety profile, it has been proposed as an alternative to SBL. **It** is essential for each center to adopt a protocol based on their experience with both techniques and to assess the need for invasive diagnostic procedures within a multidisciplinary committee (MDC) to ensure appropriate case selection.

Genetic testing

The familial aggregation is one of the most robust pieces of evidence supporting a genetic predisposition to pulmonary fibrosis (PF). It is also considered the most significant risk factor for the development of the disease. Published case series reports the presence of vertical transmission with an autosomal dominant inheritance pattern in 80% of cases and indicate that at least 20% of patients with IPF have a first-degree relative affected by some form of ILD[18]. Familial PF (FPF) is defined by the presence of at least two cases of IPF in a family. The age of onset is earlier than in non-familial forms of PF, and clinical presentation is heterogeneous, even among members of the same family and regardless of the associated genetic variant. Importantly,

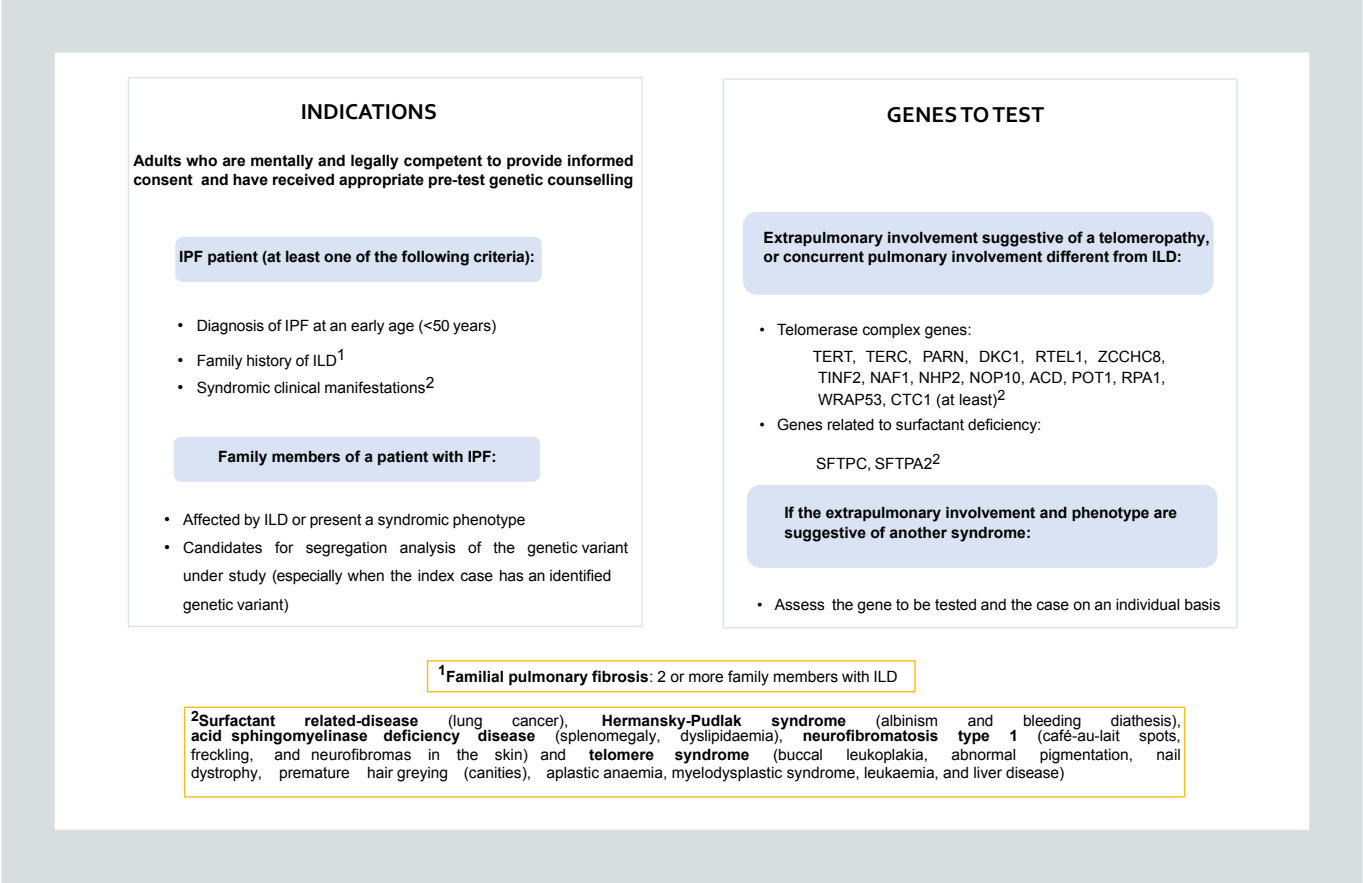

Figure 3. Genetic testing in IPF. ILD: interstitial lung diseases; IPF: idiopathic pulmonary fibrosis; ERS: European Respiratory Society.

family history is a factor of poor prognosis, regardless of the type of ILD and the age at diagnosis. The UIP pattern is the most frequent radiological and histopathological pattern. Some patients may have extrapulmonary involvement, especially when fibrosis occurs in a syndromic context[18].

Genetic studies conducted on both sporadic and familial cases of IPF have reported rare and common variants in genes involved in various pathogenic pathways[19-21]. Although genotype-phenotype correlations in PF are limited, genetic testing can, for certain patients and in an appropriate clinical context, provide valuable information to (1) stratify risk and predict disease progression, particularly in cases with telomere dysfunction; (2) optimize management of comorbidities, especially post-lung transplantation, in patients with telomere dysfunction; (3) assess potential extrapulmonary involvement associated with PF; (4) establish a molecular diagnosis in a minority of syndromic cases; and (5) support familial risk stratification when relatives are candidates for genetic testing.

Recommendations for genetic testing have been outlined in two international multidisciplinary consensus statements: the first published by the *Pulmonary Fibrosis Foundation*[22], and the second by the *ERS*[23] (Fig. 3). A multidisciplinary evaluation is essential to interpret the molecular context of the variant in relation to the patient's clinical and familial background.

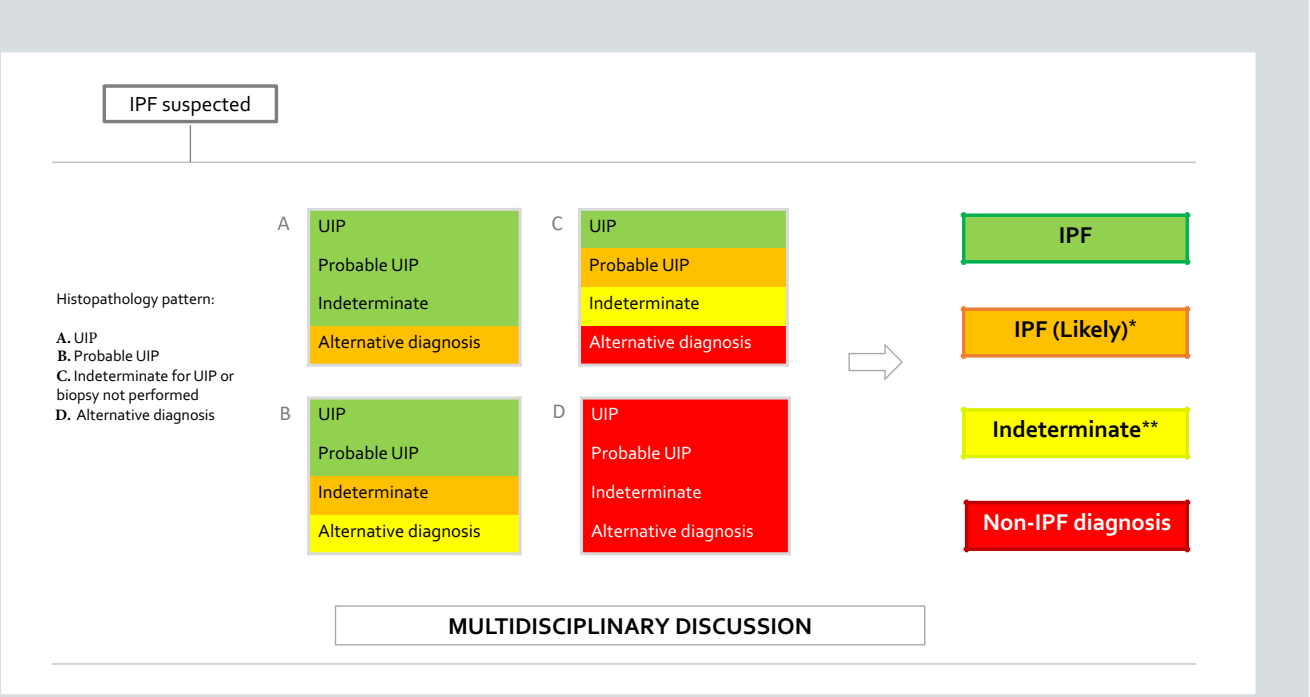

Figure 4. Diagnosis of IPF based on HRCT and histopathological patterns (*adapted from reference 6*). *IPF is the likely diagnosis if any of the following features are present: 1) moderate to severe traction bronchiectasis and/or bronchiolectasis (defined as mild traction bronchiectasis and/or bronchiolectasis in four or more lobes, including the lingula as a lobe, or moderate to severe traction bronchiectasis in two or more lobes) in a man > 50 years old or in a woman > 60 years old; 2) extensive reticulation (> 30% on HRCT) and age > 70 years old; 3) increased neutrophils and/or absence of lymphocytosis in BAL fluid, and 4) multidisciplinary discussion produces a confident diagnosis of IPF. **Indeterminate for IPF: 1) without an adequate biopsy remains indeterminate and 2) with an adequate biopsy may be reclassified to a more specific diagnosis after multidisciplinary discussion and/or additional consultation. IPF: idiopathic pulmonary fibrosis; BAL: bronchoalveolar lavage; HRCT: high-resolution computed tompography; UIP: usual interstitial pneumonia.

Multidisciplinary teams

Several studies have shown that the interaction between clinicians, radiologists, and pathologists improves diagnostic yield compared to any single test alone. For this reason, international consensus guidelines have established that the diagnosis of IPF should be made through the evaluation by an MDC[1]. However, the structure, function, and objectives of the MDC are not standardized. Nevertheless, the following conditions are generally accepted[24]: (1) the core multidisciplinary team should include a pulmonologist, radiologist, and pathologist with specific expertise in ILD, as they are fundamental to the diagnostic process. A specialized ILD nurse should also attend. The participation of rheumatologists and internists is considered positive, especially in cases where SAD is suspected. In addition, the involvement of the bronchoscopist and a thoracic surgeon should be considered in cases where invasive diagnostic options need to be discussed; (2) the MDC should have adequate space and time to meet regularly, depending on clinical demand; sufficient time should be allocated to each case to allow for a thorough review of the available tests and to promote dialogue among participants; and (3) the MDC's decisions should be documented in the medical record.

Diagnostic criteria

According to the most recent international clinical practice guidelines, the diagnosis of IPF requires the exclusion of other known causes of ILD. Once these have been ruled out, the combination of the radiological pattern on HRCT and histopathological findings (when histological sampling is indicated) allows for the diagnosis of IPF or an alternative entity. The MDD of clinical, radiological, and histopathological findings currently represents the *gold standard* for establishing a definitive diagnosis of IPF[6] (Fig. 4).

TREATMENT OF IPF

Figure 2 outlines the main components of IPF therapy.

Pharmacological treatment

Clinical practice guidelines and international consensus, based on scientific evidence, consistently support the use of antifibrotic drugs for the treatment of IPF[6,25,26]. These medications are classified as orphan drugs by the European Medicines Agency.

Pirfenidone

Pirfenidone is an antifibrotic and anti-inflammatory agent that was approved for the treatment of IPF in Europe in 2011 and in the United States in 2014. It is a pleiotropic molecule that attenuates fibroblast proliferation and extracellular matrix accumulation by inhibiting cytokines such as transforming growth factor-β and platelet-derived growth factor (PDGF), and by blocking the release of pro-inflammatory cytokines (tumor necrosis factor-α, interleukin-1 [IL]-1, IL-6, IL-8, and IL-12), while simultaneously increasing the expression of the anti-inflammatory cytokine IL-10[27].

Pirfenidone was evaluated in patients with IPF across three multinational, randomized, double-blind, placebo-controlled clinical trials: CAPACITY 1 and 2 and ASCEND[28,29]. These phase III clinical trials assessed the efficacy of pirfenidone in patients with IPF who had a forced vital capacity (FVC) > 50% predicted and a diffusion capacity for carbon monoxide (DLCO) > 35% predicted (CAPACITY) or > 30% predicted (ASCEND). Patients treated with pirfenidone showed less decline in lung function (FVC and DLCO), with a slower disease progression and a reduction in mortality[29-31]. Pirfenidone is considered a safe treatment and is generally well tolerated. The most frequently reported adverse effects (AEs) are gastrointestinal and skin-related effects. Table 1 shows the posology, main AEs, contraindications, special populations, and precautions for use of pirfenidone.

During treatment with pirfenidone, it will be avoided to administer drugs or combinations of drugs that are moderate or potent inhibitors of CYP1A2 and together with one or more of the cytochromes P450 isoforms involved in pirfenidone metabolism (i.e., CYP2C9, 2C19, 2D6, and 2E1).

Nintedanib

Nintedanib is an antifibrotic treatment that was approved in the USA for the treatment of

Table 1. Adverse effects, contraindications, and precautions for use of antifibrotic medications

	Pirfenidone	Nintedanib
Posology	**801 mg orally every 8 h**	**150 mg orally every 12 h**
Very common AEs (≥ 1/10) Common AEs (≥ 1/100 to < 1/10)	Dyspepsia, nausea, vomiting, diarrhea, constipation, gastro-esophageal reflux, weight loss, decreased appetite, rash, headache, dizziness, fatigue, insomnia, arthralgia Increased ALT, AST, GGT, gastritis, flatulence, abdominal distension, photosensitivity reaction, pruritus, rash, dry skin, hot flush, myalgia, somnolence.	Diarrhea, nausea, abdominal pain Increased ALT, AST, GGT, vomiting, weight loss, decreased appetite, dehydration, rash, bleeding, headache.
Contraindications and precautions	Hypersensitivity to pirfenidone or any excipients, history of angioedema with pirfenidone, concomitant use of fluvoxamine, severe HI or end-stage liver disease, RI (CrCl < 30 mL/min), or dialysis CrCl 30-50 mL/min: use with caution Mild-to-moderate HI: use with caution.	Pregnancy, hypersensitivity to nintedanib, peanut, soy, or excipients Patients ≥ 75 years may need a dose reduction to manage AEs CrCl < 30 mL/min: no data Mild HI: 100 mg twice daily, moderate and severe: not recommended (no data available).

Prevention and monitoring of AEs:
Perform liver function tests (ALT, AST, and bilirubin) before starting treatment, then monthly for 6 months, and every 3 months thereafter.
Advise patients to avoid alcohol and other hepatotoxic substances.
Take antifibrotic medications with food to improve tolerability and reduce gastrointestinal side effects.
Pirfenidone: Initiate treatment using a gradual dose titration schedule. Avoid or minimize exposure to sunlight and sunlamps, use broad-spectrum sunscreen, wear protective clothing, and avoid other photosensitizing drugs.
AEs: adverse effects; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: γ-glutamyl transferase; HI: hepatic impairment; RI: renal impairment; CrCl: creatinine clearance.

IPF in 2014 and in Europe in 2015. Nintedanib is a pleiotropic tyrosine kinase inhibitor, with its main target being the small molecule tyrosine kinase receptors, especially PDGF receptors α and β, fibroblast growth factor receptors, and vascular endothelial growth factor receptors (VEGFR). These receptors play a crucial role in regulating cellular processes such as cell proliferation, differentiation, and angiogenesis[32,33].

The clinical efficacy of nintedanib in IPF patients has been studied in two identical phase III, randomized, double-blind, placebo-controlled trials over 52 weeks: INPULSIS-1 and INPULSIS-2. In both studies, nintedanib significantly reduced the rate of FVC decline compared to placebo, indicating a slowing of disease progression. Moreover, a higher proportion of patients treated with nintedanib showed < 5% absolute loss in predicted FVC compared to placebo. Similar results were observed using a conservative 10% threshold. In INPULSIS-2, there was a significant increase in the time to first exacerbation and less deterioration in QoL[32]. Furthermore, the benefit of nintedanib in IPF patients is independent of the initial FVC[34-37], the presence or not of associated emphysema[38], and the Charlson comorbidity index[39].

Real-world studies support the efficacy and safety of nintedanib observed in clinical trials. The most frequently reported AEs included diarrhea, nausea and vomiting, abdominal pain, decreased appetite, decreased weight, and increased hepatic enzymes (Table 1). It is important to note that although VEGFR inhibition may increase the risk of bleeding, patients with a high bleeding risk were excluded from clinical trials. Real-world studies have reported minimal bleeding events, even among patients receiving anticoagulants or antiplatelet therapy[40]. Currently, there is no strong evidence to contraindicate nintedanib in such patients; however, an

individual risk-benefit assessment is advised, along with close monitoring. No bleeding episodes have been documented in patients receiving nintedanib in combination with direct oral anticoagulants. Patients with recent cardiovascular events were excluded from clinical trials. In the INPULSIS study (52 weeks), the rate of cardiac events was similar between patients on nintedanib and those on placebo (10% vs. 10.6%). In real-world settings, few serious cardiovascular events have been reported[41]. If signs or symptoms of acute myocardial ischemia occur, temporary discontinuation of nintedanib should be considered to prioritize acute care.

These are the considerations for initiating and monitoring antifibrotic therapy: (1) the indication for and monitoring of antifibrotic treatment should be managed by healthcare professionals with expertise in ILDs; (2) antifibrotic therapy should be considered from the time of diagnosis in all patients with IPF, including those patients with preserved FVC; these patients may exhibit abnormalities in other parameters, such as DLCO, exercise-induced desaturation, or symptoms[42]; (3) several factors should be considered when initiating antifibrotic therapy, including disease severity, prognosis, age, comorbidities, concomitant medications, and patient preferences; (4) when selecting an antifibrotic agent, clinicians should take into consideration smoking status, concomitant medications (particularly antiplatelet or anticoagulant therapy), presence of emphysema or other comorbidities, and sun exposure, as well as the patient's preferences; (5) AEs should be prevented, closely monitored, and identified early to avoid progression and support treatment adherence; the benefits of therapy and its impact on the patient's QoL should always be assessed (Table 1).

Home oxygen therapy

Home oxygen therapy is a fundamental component in the treatment of IPF since, as the disease progresses, patients tend to develop hypoxemia initially only during exertion and subsequently chronic respiratory failure.

Clinical practice guidelines recommend prescribing long-term oxygen therapy (LTOT) for patients with IPF who have severe chronic resting room air hypoxemia, administered for at least 15 h/day (strong recommendation and very low-quality evidence). This recommendation is based on extrapolated data obtained from patients with chronic obstructive pulmonary disease, in whom LTOT has been shown to reduce mortality, relieve dyspnea, improve QoL, and potentially prevent organ dysfunction associated with sustained hypoxemia, such as pulmonary hypertension[1,43].

Severe exercise-induced hypoxemia during exertion ($SpO_2 \leq 88\%$) is associated with the presence of pulmonary hypertension and an increased risk of mortality in patients with ILDs[44]. Supplemental oxygen has been shown to improve exercise capacity in IPF patients with exertional desaturation when compared to placebo air[45]. In a single 2-week crossover clinical trial of 84 patients with fibrotic ILD and $SpO_2 \leq 88\%$ during the 6-min walk test (6MWT), ambulatory oxygen was found to improve QoL when compared to placebo[46]. Further studies are needed to investigate the long-term impact of ambulatory oxygen on daily physical activity and mortality. The recommendation for

prescribing ambulatory oxygen in patients with IPF who have severe exertional room air hypoxemia is conditional and based on low-quality evidence[1,43]. Therefore, in these cases, the indication should be individualized, considering the preferences of the patient and their ability and desire for mobility.

Pulmonary rehabilitation (PR)

Two systematic reviews have concluded that PR is a safe and effective treatment for patients with IPF. This intervention provides significant benefits, such as increased exercise capacity, improved QoL, and reduced dyspnea; effects that can be maintained for up to 12 months after initiating the program[47,48]. However, the impact of PR on long-term survival and lifestyle changes remains uncertain. The 2011 international IPF guidelines made a weak recommendation based on low-quality evidence, suggesting that most patients with IPF should be included in PR programs and incorporating it into the non-pharmacological management scheme of these patients[1]. The 2022 update of these guidelines maintains that PR should be part of the standard management of these patients[6]. Therefore, inclusion in PR programs should be offered to all patients with IPF who are likely to benefit, with the aim of relieving dyspnea, improving exercise tolerance, and QoL.

Management of respiratory symptoms

The management of respiratory symptoms should begin at the time of diagnosis and be adapted to the patient's needs throughout the course of the disease. In addition, it is important to identify intercurrent conditions and comorbidities that may also contribute to clinical deterioration in these patients.

Dyspnea

Dyspnea is the most common and often the initial symptom experienced by patients with IPF, and it significantly affects their QoL[49]. Its etiology includes reduced lung compliance, loss of lung volume, increased dead space ventilation, increased respiratory drive, impaired gas exchange, and the presence of pulmonary hypertension[50].

Although antifibrotic treatments have been shown to slow the decline of lung function, they have not demonstrated any effect on dyspnea. Current recommendations include the use of morphine for the treatment of dyspnea related to IPF due to its proven efficacy in chronic respiratory diseases in general[51]. Opioids act on the central and peripheral nervous system receptors, reducing anxiety, modulating the central perception of dyspnea, and decreasing the respiratory drive[50,52]. Current evidence on the efficacy of oral morphine as a treatment for dyspnea and its safety in patients with IPF is based on retrospective studies that include small patient samples[50,52]. Oxygen therapy has been proposed as a potential treatment to reduce dyspnea during exertion in patients who present with exertional hypoxemia[53].

Cough

Cough affects 50-80% of patients with IPF and has been identified as an independent

factor in disease progression[54]. The presence of chronic cough in IPF patients can severely impact their QoL due to its effects on sleep disturbances, speech limitations, or causing significant desaturation, as well as musculoskeletal pain or urinary incontinence. The mechanisms of cough in IPF are not fully understood. It is postulated that these patients have an increased sensitivity of the cough reflex, which could result from increased traction forces affecting stretch receptors; other possible mechanisms may involve the destruction, due to fibrosis itself, of inhibitory nerves or overstimulation of the vagus nerve[55].

Current guidelines recommend considering opioid medications (morphine) or neuromodulators such as gabapentin[56,57]. However, this recommendation is based on limited clinical trials with a very small sample of patients with IPF. A recent clinical trial demonstrated a reduction in cough with a dose of 10 mg of morphine every 12 h, with an improvement in QoL[57]. Thalidomide, a potent immunomodulatory drug, has demonstrated a significant improvement in cough-related QoL in patients with IPF[58]. Despite this, its use is not recommended by expert groups due to its side effects, reported in more than 70% of patients, some of which are potentially serious, such as asymptomatic bradycardia. This drug is not available in our country. Finally, a nebulized formulation of sodium cromoglicate has shown reductions in cough frequency, but without improvement in QoL or cough severity in IPF patients[59]. Currently, a phase II clinical trial with nalbuphine is underway for the treatment of cough in IPF.

Lung transplantation

ILD is currently the leading cause of lung transplantation worldwide[60]. Due to the unpredictable clinical course and poor prognosis of IPF, early referral for lung transplant evaluation is recommended[60]. For patients with IPF on the lung transplantation waiting list, antifibrotic therapy may be continued until transplantation[61]. The most recent consensus of the International Society for Heart and Lung Transplantation provides the following recommendations regarding the timing of referral for lung transplantation evaluation in patients with ILD[60]: at the time of diagnosis, even if a patient is being initiated on therapy, for histopathological UIP or radiographic evidence of a probable UIP or definitive UIP pattern; when FVC < 80% predicted or DLCO < 40% predicted, in patients requiring supplemental oxygen, either at rest or on exertion; with one of the following in the past 2 years: relative decline in FVC > 10%, DLCO > 15%, or FVC > 5% in combination with worsening of respiratory symptoms or radiographic progression.

Palliative care

The benefits of palliative care in progressive chronic diseases are widely recognized[62]. However, referral to palliative care for patients with advanced pulmonary diseases often occurs late[63]. Specifically, in IPF, 71% of patients are referred during the last month of life[64]. The unpredictable course of the disease is likely one of the reasons why most IPF patients die in hospital settings, undergoing life-prolonging procedures[65]. Conversely, an excessively early referral, when the disease is

still mild, may negatively impact short-term QoL, possibly due to increased anxiety or depression[66]. Currently, there are no clearly established criteria for the optimal timing of palliative care initiation in patients with IPF; however, the latest ERS clinical practice guideline recommends considering referral to palliative care whenever the patient or their caregiver presents with unmet physical, psychological, social, or spiritual needs[67].

Early inclusion of patients with advanced IPF in a multidisciplinary palliative care program can facilitate adequate symptom control, provide psychological support, and assist in end-of-life decision-making, with the goal of preserving QoL throughout the disease course. This process should always be coordinated with specialized nursing care responsible for case management.

CONCLUSION

IPF is a progressive fibrotic disease with a poor prognosis. Despite the availability of antifibrotic therapies that can slow disease progression, treatment options remain limited. Early diagnosis, multidisciplinary evaluation, and timely initiation of antifibrotic therapy are essential to improving outcomes and, therefore, require greater attention in the management of patients. A holistic therapeutic approach to IPF is essential, integrating antifibrotic therapy with supportive and non-pharmacological interventions such as supplementary oxygen, PR, symptom control strategies, education, and palliative care.

CRAMPID group

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CONFLICTS OF INTEREST

None.

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Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

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