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EDITORIAL

Importance of early diagnosis and treatment in idiopathic pulmonary fibrosis

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1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a rare disease characterized by chronic, progressive, and irreversible interstitial lung fibrosis of unknown cause [1,2]. Main symptoms and signs include dyspnea, cough, inspiratory crackles, and finger clubbing [1,2]. Natural history differs greatly between patients but involves a decline in lung function that worsens quality of life and eventually leads to death. From the time of diagnosis, the median estimated survival time is 2–5 years [1,2].

IPF is difficult to diagnose, and a delay between the onset of symptoms and accurate diagnosis is frequently observed [3–5]. IPF incidence and prevalence are increasing in recent years, which can be attributed to the optimization of diagnosis and the aging of the population [1,6].

Since IPF is a fatal disease, a precise and early diagnosis is highly important. The relevance of avoiding risk factors and the availability of anti-fibrotic treatments that slow disease progression makes early diagnosis and therapeutic management more clinically relevant than ever [2,3,7].

1.1. Challenges in the diagnosis of IPF

Despite the advances provided in the last update of diagnostic criteria [7], IPF remains challenging to diagnose [3]. A discussion of clinical, radiologic, and histopathologic evidence in an expert multidisciplinary team (MDT) experienced in interstitial lung diseases (ILD) improves diagnostic accuracy and is therefore recommended [1,2]. In 2011, a multinational European survey estimated the median time of delay between symptom onset and diagnosis in 1.5 years [4]; however, a recent US survey showed that 59.8% of IPF patients experienced a diagnostic delay of >2 years [5]. IPF presents with general respiratory symptoms, which can lead to a significant amount of patients being initially misdiagnosed with asthma, chronic obstructive pulmonary disease (COPD), or pneumonia, among other diseases [3,4]. In this regard, detection of velcro-like crackles during chest auscultation, which are strongly associated with the presence of lung fibrosis, has been proposed as a feasible and sensitive measure to improve early detection [2]. However, most patients who refer the first symptoms at the primary care physician are symptomatically treated, and only when no improvement is warned, are referred to the pulmonologist [4,5]. Further differential diagnosis involves a thorough clinical examination and exhaustive exploratory tests to exclude similar fibrotic ILD [1–3]. If the pulmonologist who receives these patients does not work in a tertiary hospital center with an ILD team, after performing respiratory complementary tests, they send the patients to the ILD reference center. Therefore, final IPF diagnosis and therapeutic management usually takes more than one year [4,5].

Diagnosis of IPF requires the presence of a pattern of usual interstitial pneumonia (UIP) on high-resolution computed tomography (HRCT), or combinations of UIP patterns on HRCT and on tissue samples from lung biopsies [1]. Limitations of this approach include moderate inter-observer agreement on HRCT, and the reliance on histological analysis of a lung biopsy for patients that present with atypical HRCT patterns [3]. Sometimes, risks of lung biopsy may exceed its benefit, compromising their accurate diagnosis [3]. Moreover, the detection of aberrant patterns on HRCT implies that IPF patients are only diagnosed after the occurrence of irreversible changes in lung architecture [3].

Finally, advances in the understanding of IPF pathogenesis and identification of molecular markers would increase early diagnostic accuracy. To date, there are no specific biomarkers with predictive diagnostic or prognostic value at diagnosis, but several clinical trials are currently testing molecular, genetic, and epigenetic markers [8]. Identification of easy-to-detect, specific biomarkers with predictive value would expedite IPF diagnosis and could serve as a prognostic tool.

1.2. Benefits of early diagnosis and treatment of IPF

The irreversible lung damage caused by disease progression underscores the importance of early treatment. Consistently, late IPF diagnosis is associated with worse prognosis. In a single-center

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prospective study, the delay in patient referral to a tertiary care center increased the mortality risk independent of age or lung function [9].

Thus, an early intervention is crucial to improve IPF prognosis. The ATS/ERS/JRS/ALAT guideline for the treatment of IPF includes recommendations for the use of nintedanib, pirfenidone, and antacid therapy, as well as of non-pharmacological treatments such as pulmonary rehabilitation, long-term oxygen therapy, and lung transplantation [1,7].

Nintedanib and pirfenidone slow disease progression in a broad spectrum of patients and have shown a reduction in mortality in clinical trials [10,11]. Moreover, recent analyses demonstrate that patients with relatively well-preserved lung function (Forced Vital Capacity (FVC) >90% predicted) also benefit from anti-fibrotic treatment [12]. An early treatment is desirable because IPF evolution is unpredictable: even in patients with slow disease progression, events that worsen disease prognosis – such as acute exacerbations– can appear [1,2,6]. Importantly, real world data from a multi-center, prospective, observational registry support the beneficial effect of anti-fibrotic therapy on survival (Hazard Ratio (HR) 0.56, 95%CI 0.34–0.92, $p = 0.022$) and transplant-free survival independent of baseline disease severity, compared to non-anti-fibrotic therapy [13].

Similarly, treatment of gastro-esophageal reflux – which is observed in a majority of patients and may contribute to disease progression – has been associated with slower disease progression [1,14]. However, recommendation of antacid therapy for IPF remains controversial, and a recent position paper of an international ILD working group highlights the need for high-quality trials that address the efficacy of antacid therapy on IPF progression [15]. In addition, early intervention could increase the efficacy of therapies such as pulmonary rehabilitation (PR) [16]. Patients with less deteriorated lung function achieve greater benefits from PR than patients with more severe disease [16] and, although the level of evidence is low, the National Institute for Health and Care Excellence (NICE) guidelines include an assessment for pulmonary rehabilitation at diagnosis [2].

1.3. Need for improved management, better coordination among stakeholders, and increasing funding

A rapid and accurate diagnosis of IPF requires a multidisciplinary discussion among physicians specialized on ILD; however, MDTs are only available in tertiary care reference centers. Thus, prompt referral from primary care or non-specialist pulmonology services to centers of expertise is essential for early diagnosis. Lack of quick referral or coordination among centers hinders rapid and accurate treatment and is detrimental to the patient [2,9]. For instance, an accurate early diagnosis prevents the misdiagnosis with COPD and treatment with corticosteroids, discouraged in IPF patients [1].

Despite the widely accepted benefits of referral to a reference center, some pulmonologists still do not seek support from MDTs for early diagnosis and treatment. In Spain, direct referral circuits are implemented in primary care centers; however, referral from local hospitals is not as efficient as it would be advisable [17]. Increased awareness of disease severity and education of health-care professionals are essential to speed referral.

In addition, a stronger information flow and support among physicians and patients would be desirable. Health-care professionals should provide information including diagnosis, prognosis, management, and current research to IPF patients in a clear and accurate manner [2]. This is crucial to manage expectations and avoid misinformation and could improve quality of life and treatment adherence through an integral multidisciplinary approach in IPF patients.

Together with quick referral, more communication and better coordination among MDTs and pulmonologists are needed in order to modify disease progression and improve patient outcome. Similarly, research on mechanisms of pathogenesis and new biomarkers for diagnosis and disease progression and large-scale cost-effectiveness studies of IPF therapies should be performed.

All these management measures translate into more funding requirements. Since IPF is a rare disease, National Health Systems (NHS) should play a main role in the funding of disease management strategies. Without NHS participation, improvement of management is compromised.

1.4. Patient perspective

Recently, a European IPF Patient Charter was developed to identify unmet needs of IPF patients across Europe [17]. There was an overall agreement regarding the need for an early and accurate diagnosis; the need for better access to treatment, holistic and palliative care; and the need to raise awareness of the disease severity and its chronic nature among patients, health-care professionals, and general population [17]. Similar results were obtained in an in-depth survey from five different European countries [4]. A general complain among IPF patients was the delay on diagnosis and the lack of detailed information delivered to the patient in a sensitive and empathetic manner [4,17]; however, patient knowledge and satisfaction were higher in those treated in reference centers [4]. Additionally, patients reported a negative impact of IPF on the quality of life in personal autonomy, personal relationships, and financial difficulties [4]. Hence, early holistic therapeutic approach would not only preserve lung function, but also translate into a better quality of life for IPF patients.

2. Conclusions

IPF is a fatal disease that requires early diagnosis performed by a MDT with expertise in ILD. Since greater benefits are achieved with early actions on patients with preserved lung function, it is necessary to improve early detection and management of IPF by identifying new biomarkers, raising awareness and educating health-care professionals and general population, and placing management strategies that facilitate quick referral to specialized centers and early and accurate treatment of IPF patients.

Rapid actions positively impact disease progression, quality of life, and emotional wellbeing of IPF patients; thus, prompt referral to ILD centers is essential and should be

carried out similarly to cancer and cystic fibrosis cases. Consequences of poor coordination among stakeholders are not only detrimental to the patients but may involve ethical and legal concerns. Accordingly, Health Authorities should help to improve management and promote research, increase funding on IPF to ensure optimal care.

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