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PROGRESSIVE FIBROSING ILD

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ABSTRACT

Progressive fibrosing interstitial lung disease (PF-ILD) is a subgroup of ILDs that present a progressive-fibrosing phenotype. Progressive fibrosis is associated with worsening respiratory symptoms, decline in lung function, limited response to immunomodulator therapies and worsening quality of life leading to early mortality. A multidisciplinary approach is essential for optimal diagnosis and management. Pirfenidone and nintedanib are the only approved drugs that shows benefit in PF-ILD. **KEYWORDS** Progressive fibrosing interstitial lung disease; PF-ILD; diagnosis; FVC decline; nintedanib; pirfenidone; efficacy

INTRODUCTION

Interstitial Lung Diseases (ILD) are a heterogenous group of infiltrative diseases that affect the lung parenchyma. Although these conditions are rare, a proportion of patients with interstitial lung diseases (ILDs), have a progressive course leading to chronic progressive fibrosis and decline in lung function constituting a diverse spectrum of diseases called progressive fibrosing ILD (PF-ILD). The common types of PF-ILD include IPF (idiopathic pulmonary fibrosis), sarcoidosis, chronic hypersensitivity pneumonitis, CTD-associated ILDs (rheumatoid arthritis-associated ILD, systemic sclerosis-associated ILD, polymyositis/dermatomyositis-associated ILD, microscopic polyangiitis-associated ILD and other CTDs-associated ILDs), occupational exposure-related lung diseases and IIPs (idiopathic interstitial pneumonias)[1]. Figure 1 shows types of interstitial lung disease (ILD) that may be associated with a progressive fibrosing phenotype[2].

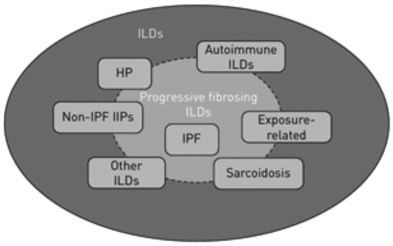

FIGURE 1 Types of interstitial lung disease (ILD) that may be associated with a progressive fibrosing phenotype. HP: hypersensitivity pneumonitis; IPF: idiopathic pulmonary fibrosis; IIPs: idiopathic interstitial pneumonias[2]. Copyright ©ERS 2019.

CLINICAL SIGNS AND SYMPTOMS

The typical presentation of an ILD is non specific and includes vague respiratory symptoms such as dyspnea on exertion or cough. Since connective tissue disease is a frequent cause of ILD, some patients may have symptoms and signs suggestive of connective tissue disease. While some may present for pulmonary evaluation with a preexisting diagnosis of connective tissue disease, pulmonary involvement maybe the first manifestation in others. In some patients, non specific symptoms such as night sweats, fever, fatigue or weight loss maybe present suggestive of an underlying inflammatory condition. Patients with systemic sclerosis may

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have a history of Raynaud's phenomenon, skin tightness and thickening, telengiectasias, digital pitting and gastrointestinal symptoms indicative of underlying esophageal dysmotility. Patients with systemic lupus erythematosus (SLE) may have malar rash, photosensitivity skin reaction or hair less. Patients with sarcoidosis may sometimes have papular eruptions, lupus pernio and erythema nodosum. Patients with dermatomyositis have dermatologic symptoms accompanied by clinical signs such as heliotrope rash, Gottron's papules or "mechanic's hands". Musculoskeletal complaints such as arthralgias, morning stiffness, joint swelling, erythema and digital deformities may suggest underlying rheumatoid arthritis. Ophthalmologic symptoms suggestive of uveitis maybe present in SLE and sarcoidosis. Presence of cardiac symptoms may suggest an advanced disease wherein cor pulmonale is present or it maybe due to cardiac involvement by the underlying disease itself. A thorough history pertaining to medications used by the patient may lead to the diagnosis of a drug-related lung disease. Exposure to organic dusts such as moldy hay, bird feathers and droppings may lead to the diagnosis of chronic hypersensitivity pneumonitis. A thorough occupational history including all jobs held in the past may lead to the diagnosis of an occupational exposure-related lung disease.

Physical examination may reveal fine, inspiratory, basilar "Velcro" crackles on auscultation and digital clubbing in some patients. Signs of pulmonary hypertension and right heart failure maybe present. Patients with connective tissue disease may have dermatologic and musculoskeletal signs.

DIAGNOSIS

The diagnosis of ILDs is usually multidisciplinary involving pulmonologists, radiologists and pathologists. Comprehensive evaluation includes clinical assessment, relevant clinical history, smoking status, lung function testing, serologic testing for underlying connective tissue disease, radiological imaging and lung biopsy, if required. In almost all cases, high-resolution computed tomography (HRCT) of the chest is the primary diagnostic tool[3]. Serological testing can be done if there is clinical suspicion of an underlying autoimmune disease or autoreactive component[4]. Lung biopsy and bronchoscopy are indicated when other assessments are inconclusive. Bronchoalveolar lavage may be needed for the diagnosis of some ILDs. Figure 2 shows an algorithm published by the ERS for diagnosing ILDs that may present a progressive-fibrosing phenotype[5].

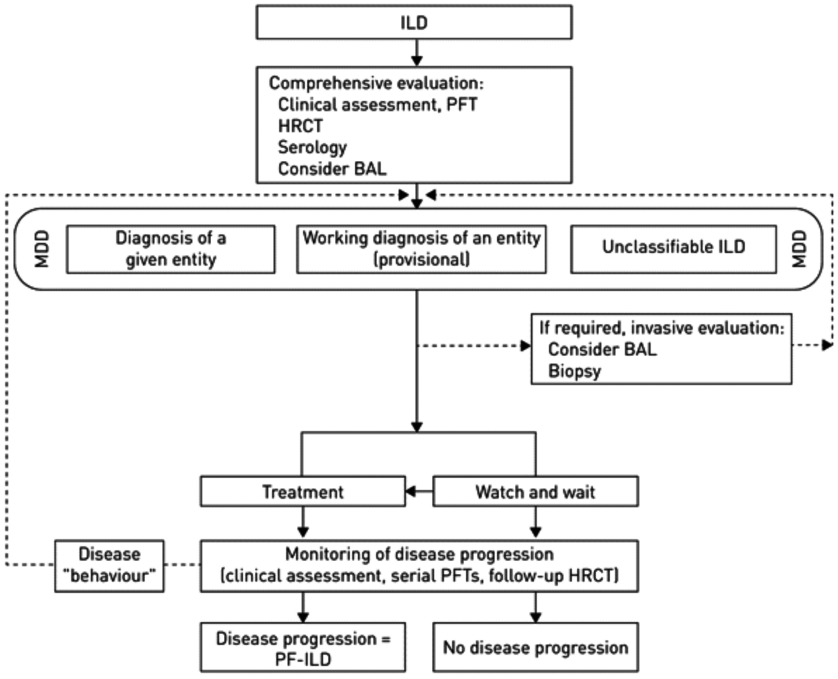

FIGURE 2 Diagnosis of fibrosing interstitial lung diseases (ILD) that may present a progressive phenotype. PFTs: pulmonary function test; HCRT: high-resolution computed tomography; BAL: bronchoalveolar lavage; MDD: multidisciplinary diagnosis; PF-ILD: progressive-fibrosing ILD[5]. Copyright ©ERS 2018.

DEFINITION OF PROGRESSIVE PULMONARY FIBROSIS (PPF):

In a patient with ILD of known or unknown

etiology other than IPF who has radiological evidence of pulmonary fibrosis, PPF is defined as at least two of the following three criteria occurring within the past year with no alternative explanation:

1. Worsening respiratory symptoms
2. Physiological evidence of disease progression (either of the following):

(a.) Absolute decline in FVC >5% predicted within 1 yr of follow-up
(b.) Absolute decline in DLCO (corrected for Hb) >10% predicted within 1 yr of follow-up

3. Radiological evidence of disease progression (one or more of the following):

(a.) Increased extent or severity of traction bronchiectasis and bronchiolectasis
(b.) New ground-glass opacity with traction bronchiectasis
(c.) New fine reticulation
(d.) Increased extent or increased coarseness of reticular abnormality
(e.) New or increased honeycombing
(f.) Increased lobar volume loss[6].

MANAGEMENT

The aim of treatment is to slow down the disease progression. Anti-fibrotics like pirfenidone and nintedanib are the mainstay of treatment in PF-ILD. Both pirfenidone and nintedanib have been approved in multiple countries (including Europe and the USA) for the treatment of IPF. Pirfenidone is an oral antifibrotic agent with anti-inflammatory properties shown to decrease disease progression in IPF, as assessed by lung function, exercise tolerance and progression-free survival[7]. Nintedanib is a triple tyrosine kinase inhibitor and has an antifibrotic effect. While there a number of clinical trials supporting the clinical benefits of anti-fibrotics like pirfenidone and nintedanib, a few of them are discussed briefly as below.

INPULSIS-1 and INPULSIS-2 are two replicate 52-week, randomized, double-blind, phase 3 trials in which a total of 1066 patients were randomly to receive nintedanib (150 mg of oral nintedanib twice daily) or a placebo. The FVC decline was −114.7 ml per year with nintedanib versus −239.9 ml per year with placebo in INPULSIS-1 and −113.6 ml per year with nintedanib versus −207.3 ml per year with placebo in INPULSIS-2. The results of the two trials showed that nintedanib reduced the FVC decline in patients with idiopathic pulmonary fibrosis. The most frequent adverse event in both the trials was diarrhea in the group of patients receiving nintedanib[8,9].

The INBUILD trial was a randomized, double-blind, placebo-controlled, phase III trial which investigated the efficacy and safety profile of nintedanib (150 mg of oral nintedanib twice daily) as compared to a placebo in 663 patients with PF-ILD other than idiopathic pulmonary fibrosis. The result of the trial showed that the FVC decline was 80.8 mL per year in the nintedanib group and 187.8 mL per year in the placebo group, resulting in a difference of 107 mL. Many different types of ILD (other than idiopathic pulmonary fibrosis) were included in INBUILD trial and they were classified into five subgroups which included idiopathic non-specific interstitial pneumonia, hypersensitivity pneumonitis, autoimmune disease–related ILD, unclassifiable ILD, and “other” fibrosing ILDs. No significant differences were observed in the efficacy of nintedanib between these disease subgroups[9,10].

Similarly in the CAPACITY and ASCEND trials, 1247 patients who were randomised to pirfenidone 2403 mg per day or a placebo. The results from the phase 3 CAPACITY and ASCEND trials showed that pirfenidone significantly reduces all-cause mortality and treatment-emergent IPF-related mortality at 1 year. Pirfenidone was found to have reduced disease progression in patients with idiopathic pulmonary fibrosis as compared with placebo[7,11].

Data on pirfenidone's efficacy in ILD other than IPF is limited. The largest trail that has been published so far concerning the efficacy of pirfenidone in ILD other than IPF is the UILD trail. It is a randomized, double-blind, placebo-controlled, 1:1, phase 2 trial in which a total of 253 patients with a progressive, fibrosing, unclassifiable ILD (uILD) were randomized to pirfenidone 2403 mg per day or a placebo for a period of 24 weeks. Since uILD is a diagnosis of exclusion after all other ILDs have been ruled out, a post-hoc data analysis from the pirfenidone in the UILD trial was performed based on the surgical lung biopsy (SLB) status. The study revealed that pirfenidone may be an effective option regardless of SLB status[9,12,13].

The RELIEF study was a randomized, double-blind, placebo-controlled, parallel phase 2b trial in which a total of 127 patients were randomized to receive pirfenidone 2403 mg per day or a placebo for 48 weeks. The pirfenidone group had a significantly lower FVC decline predicted compared with the placebo group. The RELIEF study was terminated prematurely due to slow recruitment and the consequent issue related to underpowering and hence the FVC trends should be interpreted with caution[9,14].

CONCLUSION

PF-ILDs are associated with progressive pulmonary fibrosis characterized by decline in lung function and worsening quality of life leading to early mortality. A multidisciplinary approach is essential for optimal diagnosis and management. Other than nintedanib and pirfenidone, no drugs are approved for the treatment of fibrosing ILDs.

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