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Progressive fibrosis in interstitial lung diseases — proposed definition and management

Abstract

Interstitial lung diseases may have an unpredictably progressive course, which is manifested as progression of pulmonary fibrosis, causing an increasing impairment of lung function affecting a poor prognosis. The possibility of an effective antifibrotic treatment is a chance for patients to slow down the progression of the disease, perhaps even extend their life. For this reason, standardization of the definition as well as identification criteria for progressive fibrosis interstitial lung disease is a method for optimizing the management in this group of patients.

Key words: interstitial lung disease, progressive fibrosis, antifibrotic treatment

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Introduction

Interstitial lung diseases (ILDs) are a heterogeneous group of diseases differing in aetiopathogenesis, clinical course and prognosis [1]. The common characteristic of some of them is the possible progressive nature of lesions that leads to advanced fibrosis that is not amenable (at a certain stage) to anti-inflammatory or immunomodulating causative treatment [2]. A classic example of progressive fibrosing interstitial lung disease (PF-ILD) is idiopathic pulmonary fibrosis (IPF). IPF is a disease of unknown aetiology (despite identification of potential risk factors) with lesions that have a morphology of usual interstitial pneumonia (UIP), which is diagnosed by ruling out other causes of the observed lesions [3, 4].

IPF has an unpredictably progressive course, which is manifested as progression of pulmonary fibrosis, causing an increasing impairment of lung function and inevitably leading to death [3–6]. The natural course of the disease is associated with a median survival (3–5 years) shorter than in the course of many types of cancer [7, 8]. Progressive pulmonary fibrosis is a characteristic encountered also in the course of other ILDs. It affects patients with hypersensitivity pneumonitis (HP), interstitial lung lesions associated with connective tissue diseases (CTD; in particular diffuse systemic sclerosis, rheumatoid arthritis, systemic myositis and other), idiopathic non-specific interstitial pneumonia (NSIP), sarcoidosis or unclassifiable idiopathic interstitial pneumonia (uILD). As demonstrated by studies in the recent years, identification of the PF-ILD phenotype and adequate therapeutic management may improve the prognosis in this patient group [9, 10].

Definition of PF-ILD

An initial attempt at defining PF-ILD with specification of its diagnostic criteria was made at the stage of clinical trials to select patients for conducting an assessment of the effect of antifibrotic treatment [9–11]. On the basis of those experiences, an international expert panel published proposed recommendations for both identification and management of patients with this phenotype of interstitial pulmonary fibrosis [2].

Until 2019, the usefulness of the antifibrotic effect in non-IPF interstitial disorders leading

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to pulmonary fibrosis was only a hypothesis (presumption) [12, 13]. Numerous trials are now ongoing, but in some of the completed ones evidence was obtained that nintedanib can effectively slow down the progression of interstitial lesions in patients with systemic sclerosis (the SENSCIS trial) as well as with other ILDs where disease progression was observed despite the existing treatment (the INBUILD trial) [9, 10]. Different eligibility criteria for patients with progressive interstitial pulmonary fibrosis were adopted in clinical trials investigating the efficacy of antifibrotic treatment. At the current stage, on the basis of the evidence that already exists, it is considered that progressive fibrosis associated with an interstitial lung disease is a situation (phenotype) in which pulmonary lesions still progress despite conventional treatment. The definition of PF-ILD should take into account the combination of aggravating lesions in the radiological image (CT), decline of lung function and clinical symptoms experienced by the patient. The role of a multidisciplinary team is emphasised – both at the stage of diagnostic work-up, determining the proper, precise diagnosis of ILD and assessment of disease progression or the lack of efficacy of the first-line treatment used, dedicated to the given diagnosis. In the case of non-IPF PF-ILD, the antifibrotic therapy should be a type of second-line treatment when progression of fibrosis is evidenced despite the use of conventional treatment [2].

The diagnosis of PF-ILD requires confirmation of disease progression during the previous 24 months of follow-up, occurring despite the use of adequate therapy. However, it worth to point out that the observation period for the PF-ILD diagnosis is not established and in clinical trials the adopted observation time was different (6–24 months).

Disease progression was defined as meeting one of the following criteria:

1. ↓ forced vital capacity (FVC) by ≥ 10% of the predicted value or
2. ↓ FVC by ≥ 5% of the predicted value with ↓lung transfer factor for carbon monoxide (TLCO) by ≥15% of the predicted value, or
3. ↓ FVC by ≥ 5% of the predicted value with ↑ respiratory symptoms, or
4. ↓ FVC by ≥ 5% of the predicted value with ↑ extent of fibrosis in high resolution computed tomography (HRCT), or
5. Severe respiratory symptoms and ↑ extent of fibrosis in HRCT [2].

Scale of the problem

The question of how many patients in clinical practice have the progressive fibrosing phenotype preoccupies the researchers concerned with this issue.

The incidence of PF-ILD is an estimate based on retrospective analyses of groups of patients with interstitial pulmonary lesions with such a course of the disease. The disease outcomes vary, which is not surprising in view of different criteria of group selection and different criteria of assessment of fibrosis progression [14–17].

In an extensive international questionnaire survey with participation of 486 specialists (243 pulmonologists, 203 rheumatologists and 40 internists), the estimated prevalence of PF-ILD was 18–32% of patients diagnosed with ILD [18]. On the basis of the obtained data, 25–50% of patients with evidence of PF-ILD do not receive pharmacological treatment and the time from symptoms onset to death was assessed as 61–80 months [18]. Failure to initiate a therapeutic intervention was explained by different issues arising from disease advancement (both mild and too severe course), intolerance of medicines and also the lack of an effective treatment [18].

In a recently published review of literature concerning this issue, the prevalence of PF-ILD was estimated as 2.2–20.0 per 100,000 in Europe and 28.0 per 100,000 in the USA, with an estimated percentage of 13–40% of ILDs cases [19].

The clinical course — the rate of decline in pulmonary function — in non-IPF PF-ILDs is similar to that of IPF, which indicates an adverse prognosis in this patient group [20]. In the INBUILD study in patients with PF-ILD with pulmonary lesions of the UIP pattern, the rate of deaths in the placebo arm was identical to that found in patients with IPF in the placebo arm in the INPULSIS studies (7.8% in a one-year follow-up) [20].

The key issue, noted on many occasions, is the lack of the generally adopted (diagnostic and therapeutic) management standard in PF-ILD patients.

Efficacy of treatment of non-IPF PF-ILD with antifibrotic agents

In randomised placebo-controlled clinical trials, nintedanib (TOMMOROW, INPULSIS-1, INPULSIS-2) and pirfenidone (CAPACITY-004, CAPACITY-006, ASCEND) were found to effectively and significantly reduce the decline in

FVC, which translates into slowing down the IPF progression [21–24]. Both medicines have been approved for the treatment of IPF, and the positive effects obtained in clinical practice, along with the trends towards prolonged survival in the treated patients with an acceptable treatment tolerability, prompted further studies in indications extended to other interstitial diseases associated with fibrosis [25–29].

So far, on the basis of the existing results of clinical trials, only nintedanib obtained an extension of its approved indications by the treatment of patients with systemic sclerosis-associated ILD (the SENSCIS study) and patients with other non-IPF interstitial lung diseases with progressive pulmonary fibrosis in their course (the INBUILD study) [9, 10].

Nintedanib is an oral tyrosine kinase inhibitor with a multitarget mechanism of action that involves inhibition of vascular endothelial growth factor receptors (VEGFR 1–3), platelet-derived growth factor receptors (PDGFR α and β) and fibroblast growth factor receptor (FGFR 1–3), which participate in the pathogenic process of fibrosis [21].

As demonstrated by post-hoc analyses of databases of marketing authorisation and post-marketing studies investigating nintedanib in IPF patients, the beneficial treatment effect is maintained in the long term, occurs regardless of disease advancement, and contributes to a reduction of the risk of sudden exacerbations and probably to extended survival of patients [25, 26, 30–35]. By analogy, similar effects against other PF-ILDs were expected.

Another antifibrotic agent — pirfenidon is also investigated in non-IPF ILDs, but so far is not registered for treatment in this indication [11].

Efficacy of nintedanib treatment of ILD associated with systemic sclerosis (SSc)

Systemic sclerosis (SSc) is a rare multiorgan autoimmune disease. It is characterised by blood vessels injury, the presence of autoantibodies and progressive fibrosis of the skin and internal organs. The clinical course may vary. It depends on the rate of development of organ complications in the individual patients [36]. Lung involvement, which unfortunately occurs in most patients, has a significant impact on the prognosis. Pulmonary fibrosis and pulmonary hypertension are the main causes of deaths related to disease progression [37]. Unfortunately, the existing anti-inflammatory and immunomodulating treatment is sometimes toxic and is not sufficiently effective — it does not stop over a long term the progression of interstitial lesions in the lungs [38–40].

In the randomised double-blind placebo-controlled SENSCIS study including a group of 576 SSc patients, nintedanib treatment (during a 52-week follow-up) was found to significantly reduce the rate of decline in pulmonary function [10]. Unfortunately, it was not found to have a beneficial effect on the skin lesions whose improvement was assessed as a secondary objective. Although in INPULSIS studies the decline in pulmonary function in the group that received placebo was more than a half lower than in the group of IPF patients treated with nintedanib (–93.3 mL *vs* –223 mL), the relative effect on the reduction of FVC decline was similar (–44% *vs* 49%, respectively). The absolute (numerical) difference in FVC decline may seem small (41 mL in favour of the nintedanib group) but it should also be considered that immunosuppressive treatment was allowed in the study group and almost a half of the patients received mycophenolate mofetil (MMF). An annual difference in FVC decline was visible in the placebo group that received MMF or not (–66.5 mL *vs* –119.3 mL) [10].

Antifibrotic treatment gave hope to SSc patients for slowing down the progression of ILD [41].

Efficacy of nintedanib treatment of ILD associated with non-IPF PF-ILD

Another double-blind placebo-controlled phase 3 study abbreviated as INBUILD included 663 patients at 15 sites around the world, with different non-IPF ILDs (including also SSc) who have developed progressive pulmonary fibrosis [9].

The inclusion criteria for the study became the basis for establishing the proposed PF-ILD definition [2]. The predominant basic diagnosis was HP, followed by autoimmune diseases, idiopathic NSIP, uIIP, and other ILDs (e.g. sarcoidosis). Also in this case a significant benefit for patients treated with nintedanib was demonstrated, in the form of a reduced FVC decline in a 52-week follow-up (–80.8 mL *vs* –187.8 mL in the placebo group). The inter-group difference was 107 mL/year (95% confidence interval [CI], 65.4–148.5; $p < 0.001$). For patients with the HRCT pattern of pulmonary lesions consistent with UIP, the difference was even larger than in the overall population and was 128.2 ml (95% CI, 70.8–185.6; $p < 0.001$) [9]. As demonstrated in a further analysis, regardless of the diagnosis, i.e. regardless of whether a patient with CTD-as-

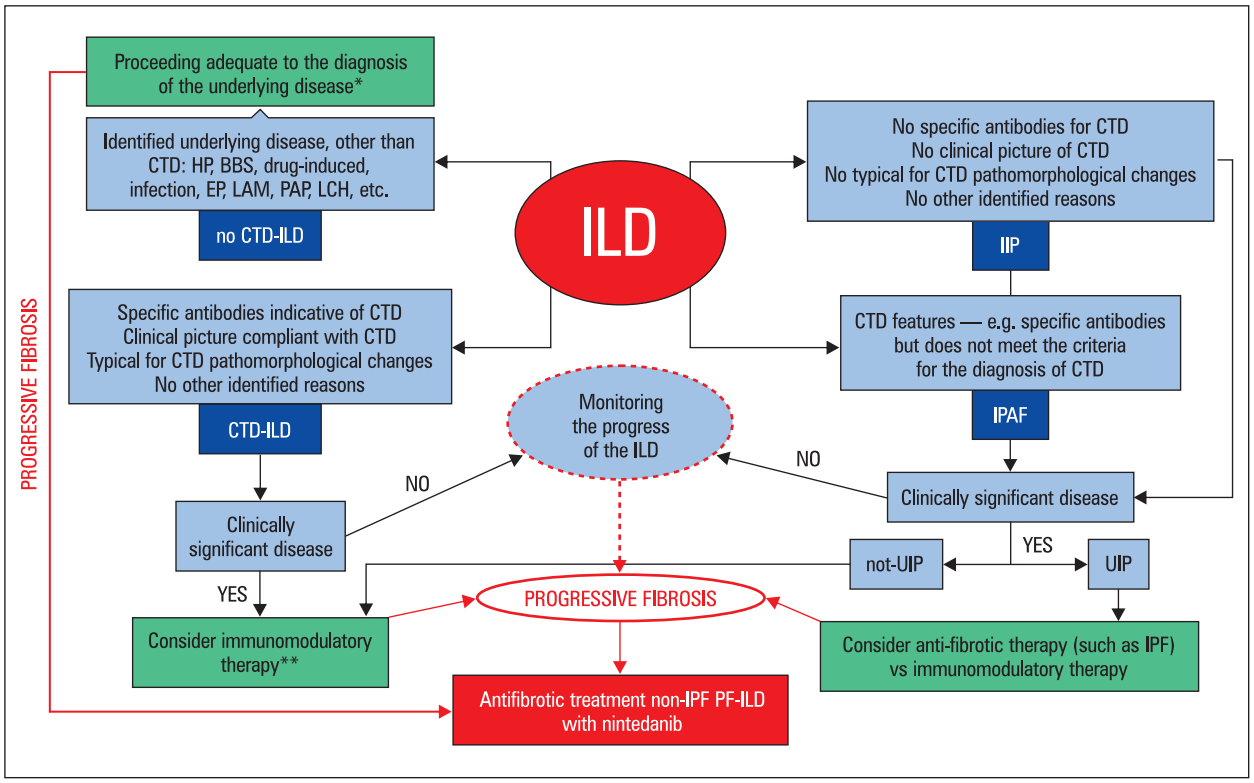

Figure 1. Proposed algorithm of diagnostic and therapeutic management of patients with ILDs (developed by the authors).

ILD — interstitial lung disease, CTD — connective tissue disease, CTD-ILD — CTD-associated interstitial lung disease, HP — hypersensitivity pneumonia, BBS – Besnier-Boeck-Schaumann's disease, sarcoidosis, EP — eosinophilic pneumonia, LAM — lymphangioleiomyomatosis, PAP — pulmonary alveolar proteinosis, LCH – Langerhans cell histiocytosis, IIP — idiopathic interstitial pneumonia, IPAF — interstitial pneumonia with autoimmune features, IPF — idiopathic pulmonary fibrosis, non-IPF — non-IPF diseases, PF-ILD — interstitial lung disease with a progressive fibrosing phenotype

*The procedure should follow the current recommendations regarding the treatment of a specific disease entity (in some situations it may be avoiding the causative factor, monitoring the progress of ILD, in others undertaking pharmacological treatment)

**The rheumatological consultation is necessary for each CTD-ILD, including an assessment of indications for treatment due to systemic disease. In the case of CTD-ILD with UIP pattern, with no indications for systemic treatment due to CTD, antifibrotic treatment can be considered as the first-line therapy.

sociated ILD, HP or with another form of PF-ILD was treated, all those patients had similar benefits from the treatment with nintedanib [42].

It seems justified to consider the antifibrotic treatment with nintedanib in all patients with PF-ILD in whom conventional treatment consistent with the standard of care dedicated to the underlying disease has failed or is contraindicated.

The proposed algorithm of diagnostic and therapeutic management is presented in Figure 1.

Safety of PF-ILD treatment with nintedanib

The antifibrotic treatment with nintedanib is associated with a risk of adverse drug reactions that nevertheless do not preclude the therapy in most cases, which has been known after the previous studies in groups of IPF patients [22, 26, 43–45].

The profile of adverse drug reactions in studies on non-IPF PF-ILDs was consistent with the previous observations. The most common adverse drug reaction was diarrhoea, observed in 66.9–75.7% of the patients [9, 10]. Elevated transaminases were found in 4.9% of the patients diagnosed with SSc in the SENSCS study and 13% of the patients in the INBILD study treated with nintedanib, and this reaction was mostly transient and reversible [9, 10]. No differences in the severity of adverse drug reactions were observed between patients with the UIP-like pattern of pulmonary lesions and patients with a different pattern [9].

The generally adopted rules that have been determined in studies and observations in patients with IPF should be used for patient selection and treatment monitoring. The possible treatment contraindications, comorbidities and potential interactions with other medicines should be taken into account. The standard therapeutic doses and methods of managing adverse drug reactions are similar as in the treatment of IPF (300 mg per day in two divided doses, and if adverse drug reactions occur, it is recommended

to use symptomatic treatment and, if necessary, to reduce the medicine dose to 200 mg per day or to temporarily interrupt the treatment).

Conclusions

The existing observations indicate that PF-ILD may affect a significant percentage of patients with ILDs. The need for defining this patient group arises mainly from the practical aspect of the demonstrated efficacy of antifibrotic treatment (currently proven for nintedanib) in patients with non-IPF ILDs associated with progressive pulmonary fibrosis.

The standardisation of the diagnostic criteria of PF-ILD would enable easier identification and selection of an adequate patient group for antifibrotic treatment.

Conflict of interest

MMM-B and WJP reports fees for lectures, consultancy and travel to medical meetings from Boehringer Ingelheim and Roche outside the submitted work.

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