New Insights on Mechanisms and Treatment in Idiopathic Pulmonary Fibrosis

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Abstract: Interstitial lung disease (ILD) represents a large group of diseases characterized by various degrees of inflammation and fibrosis, with progressive scarring of the interstitium, the tissue around the air sacs, leading to lung stiffness and restrictive pattern. Depending on the main pathological process, ILD extends from inflammatory type diseases, follicular bronchiolitis being the most representative, to fibrotic type diseases, with idiopathic pulmonary fibrosis (IPF) being the most common and studied. The aim of the article is to review the current knowledge on pathogenesis, diagnosis and treatment in IPF based on research results and recent trials data. Nintedanib and pirfenidone are pointed out as the only two conditional recommended drugs for IPF by the current international guidelines.

Keywords: Idiopathic pulmonary fibrosis, usual interstitial pneumonia, nintedanib, pirfenidone.

1. INTRODUCTION

IPF belongs to idiopathic interstitial pneumonias (IIPs), a group of diffuse lung diseases of unknown etiology, that primarily involves the pulmonary interstitium, the area between the alveolar epithelium and the capillary endothelium, the basement membrane, as well as the septal and bronchovascular tissues that build up the fibrous framework of the lung [1]. The primarily interstitial processes will frequently involve the airways, vasculature and alveolar airspaces [1].

2. EPIDEMIOLOGICAL DATA

IPF is a specific form of progressive, debilitating and ultimately fatal fibrosing interstitial pneumonia of unknown causes, occurring in older adults, limited to the lung, and characterized by the radiological and histopathological pattern of usual interstitial pneumonia (UIP) [2]. Its natural course is highly variable and difficult to predict in individual cases; the median survival time after diagnosis is of 2-3 years [2, 3], with a mortality rate at 5 years of 65%. Some patients experience a rapid decline, some have a rather slow progress, and some patients have periods with relatively stability interspaced by acute deterioration in respiratory function. If these acute deteriorations have no identifiable causes and occur at any time during the course of the disease without any warning, they are known as acute exacerbations [2, 3]. Despite wide variations of incidence and prevalence, IPF has an estimated incidence of 0.6 to 17.4 per 100.000 person years and a prevalence ranging from 0.7 to 63.0 per 100.000 [3]. Acute IPF exacerbations are rare, risky and devastating events significantly impacting prognosis for all patients, with an important morbidity and mortality [2, 3]. Episodes like this occur in up to a third of patients with IPF per year [3], with a 5-10% estimated annual incidence; 50% of patients admitted for an acute IPF exacerbation die during hospitalization [2].

Acute exacerbations are defined as events meeting all the following criteria: unexplained worsening or development of dyspnea within the previous 30 days; new diffuse pulmonary infiltrates visualized on chest radiography, high resolution computed tomography (HRCT) or both, or the development of parenchymal abnormalities with no pneumothorax or pleural effusion (new ground-glass opacities) since the preceding visit; and exclusion of any known cause of acute worsening, including infection, left heart failure, pulmonary embolism, and any identifiable cause of acute lung injury, as assessed by clinical routine and microbiologic studies [4].

Multimorbidities are common in these old people with a median age of 66 years at diagnosis of IPF. The prevalence and impact of comorbidities on the clinical course of IPF is still unclear; the mortality was highest among patients with IPF and lung cancer [5]. A systematic literature review made in 2015 found the most reported respiratory and nonrespiratory comorbidities [5]. First were represented by chronic obstructive pulmonary disease, pulmonary hypertension, obstructive sleep apnea, lung cancer and pulmonary embolism. The nonrespiratory comorbidities are gastro-esophageal reflux disease (the antiacid

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therapy is associated with longer survival), cardio-vascular comorbidities (e.g., arrhythmias, cardiac failure, ischemic heart disease, systemic arterial hypertension, cerebrovascular disease and stroke) and metabolic comorbidities (e.g., diabetes, hyper-cholesterolemia /hyperlipidemia and weight disorders).

3. IPF PATHOGENESIS

Current evidences suggest that lung fibrosis occurs as a result of an aberrant proliferation of fibrous tissue and tissue remodeling due to the abnormal function and signaling of alveolar epithelial cells and interstitial fibroblasts [3, 4]. Alveolar epithelial cell senescence /dysfunction, interstitial fibroblast activation and myofibroblast differentiation lead to excessive synthesis and deposition of collagen and remodeling of the extracellular matrix [3]. The activation of cell-signaling pathways through tyrosine kinases such as fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) is implicated in the IPF pathogenesis [4]. These mechanisms are apparently related to aging and subsequent changes in cellular function. It seems that genetics plays a central role as well, with some genetic variants strongly associated with the risk of IPF, as mutations in the telomerase gene family and polymorphism in MUC5B (Mucin 5B, Oligomeric Mucus/Gel-Forming) gene [3] and ELMOD2 (ELMO domain-containing protein 2) gene [1] as well.

4. PRINCIPLES OF DIAGNOSIS

The deposition of excessive scar tissue within the lungs leads to cough, progressive breathlessness and ultimately to respiratory failure and death [4, 6]. The histopathological specific pattern is of usual interstitial pneumonia (UIP) on the lung biopsy pieces [1], with temporally and spatially heterogeneous fibrosis, honeycombing and fibroblastic foci. A progressive loss of lung function, a decline in forced vital capacity (FVC) is consistent with disease progression and is predictive of reduced survival time [4]; this restrictive defect is accompanied by decreased diffusion capacity (DLCO). Chest radiography is the first test to suggest interstitial lung disease, but it can be normal in up to 10% of patients, especially in early stages. In ILD can be detected the next radiological pattern: reticular-nodular shadowing, ground-glass at onset or honeycomb appearance in more advanced cases; fibrosis should be differentiated from consolidation and oedema [7].

High resolution computed tomography (HRCT) of the chest is the preferred radiological test and it enhances approximately 10 times the conventional chest CT resolution, allowing to detect details otherwise not visualized. The radiological appearance is not enough for diagnosis and it should be interpreted in the clinical context, keeping in mind the temporal profile of the IPF process. HRCT in IPF shows a honeycomb lung destruction with basal and peripheral predominance [3, 8]. Additionally they may be considered some other two aspects: first, the presence of reticular abnormality and traction bronchiectasis consistent with fibrosis with basal and peripheral predominance; secondly, atypical features suggestive for alternative causes absent, specifically nodules and consolidation; ground glass opacity if present, is less extensive than reticular opacity pattern [3, 8].

The diagnosis of IPF can be made by exclusion of other common cause of ILD (e.g., domestic and occupational environmental exposure, connective tissue disease, and drug toxicity), by the presence of UIP pattern on HRCT in the absence of surgical lung biopsy, or by careful integration of HRCT and surgical lung biopsy findings [2].

5. IPF TREATMENT

The aim of treatment for many years and patients was symptom control in palliation and only recently few drugs became available [6]; solely pirfenidone and nintedanib produce a statistically significant slowing in the rate of FVC decline compared with placebo [6], which is consistent with a slowing disease progression [4]. In October 2014 the US Food and Drug Administration (FDA) has approved the first drugs for the treatment of IPF in the USA: nintedanib (Ofev, Boehringer Ingelheim Pharmaceuticals) and pirfenidone (Esbriet, InterMune). Pirfenidone was already licensed for the treatment of IPF in Europe in 2011 [6], while nintedanib was approved as a treatment for IPF in Europe only in January 2015 [3]. In indirect comparison nintedanib was associated with better results on slowing the decline in FVC than pirfenidone; all-cause mortality rates showed trends in favour of pirfenidone, but not statistically significant; it seems that both drugs have little effects on quality of life [6]. Treatment duration ranged between 8 to 16 months, with a median follow up of approximately 12 months [6]. Of note, these treatments do not stabilize or reverse the decline in IPF and more studies are requested.

The official 2015 ATS/ERS/JRS/ALAT clinical practice guidelines on the treatment of IPF [9] made conditional recommendation for the use of nintedanib and pirfenidone and represent the first time that the panel has recommended an IPF-specific therapy. Comparing to the 2011 guidelines, they have been made strong recommendation against use for: anticoagulation (warfarin); combination prednisone + azathioprine + N-acetylcysteine (there are new findings that the regimen increases mortality and hospitalization); ambrisentan (selective endothelin receptor antagonist); imatinib (a tyrosine kinase inhibitor with one target). They have been made conditional recommendation against use for dual endothelin receptor antagonists (macitentan, bosentan) and phosphodiesterase-5 inhibitor (sildenafil) [9, 10]. Amongst unchanged recommendations, there are conditional recommendations for the use of antiacid therapy and N-acetylcysteine monotherapy and they have been deferred up to new evidences the recommendations regarding: the anti-pulmonary hypertension therapy for IPF-associated pulmonary hypertension and the single versus bilateral lung transplantation [9, 10].

6. NINTEDANIB

Nintedanib is an indolinone derivate, an intracellular tyrosine kinases inhibitor with multiple targets, that blocks the autophosphorylation of vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and FGF (fibroblast growth factor) tyrosine kinase receptors [3, 10]. The drug competitively binds to the adenosine triphosphate binding pocket of these receptors, blocking substrate binding and consequently inhibiting a number of downstream signaling cascades. It specifically acts on FGF receptor 1, 2 and 3, PDGF receptor α and β, and VEGF receptor 1, 2 and 3 [3]. It reduces processes active in fibrosis as fibroblast proliferation, migration, differentiation and survival; secretion of extracellular matrix and angiogenesis in the lung [3].

The efficacy and safety administration of nintedanib in patients with IPF were investigated in phase II of 12-month TOMORROW trial and in two replicate 52-week randomized, placebo-controlled phase III trials named INPULSIS trials. The results of dose-finding TOMORROW trial suggested that nintedanib at a dosage of 150 mg twice daily slows the IPF progression by reducing the annual rate of decline in forced vital capacity (FVC), fewer acute exacerbations and preservation of health-related quality of life assessed with St George's Respiratory Questionnaire (SGRQ), together with manageable side effects [3].

To be eligible to enter the INPULSIS trials, patients had to be over 40, to have a FVC of 50% of predicted or higher, a diffusing capacity of the lung for carbon of 30-79% of predicted value and a HRCT of the chest performed in the last 12 months; additionally, ratio of FEV1/FVC was at least 0.7 (FEV1 – forced expiratory volume in one second). The trials also included patients with minimal impairment of lung function (FVC > 90% predicted), no honeycombing on HRCT and concomitant emphysema [8]. The primary end-point in both INPULSIS trials was the influence over the annual rate of decline in FVC (ml/year). Nintedanib has slowed in both trials the annual rate of decline in FVC compared with placebo; it slowed disease progression in a broad range of IPF patients types, with an approximately 50% reduction in the decline of lung function, regardless of the lung function at baseline [8]. In INPULSIS-1 the adjusted annual rate of decline in FVC was -114.7 ml/year versus -239.9 ml/year with placebo, while in INPULSIS-2 the values were -113.6 ml/year with nintedanib and -207.3 ml/year with placebo [3, 4].

Nintedanib has an acceptable safety profile and a manageable tolerability profile. The most frequent adverse effect is diarrhea, reported in INPULSIS trials by 62.4% patients compared with 18.4% in the placebo group. Almost all events were mild or moderate in intensity, and only 4.4% of patients treated had to discontinue medication due to diarrhea. Other reported side effects were nausea, nasopharyngitis, cough, progression of IPF, bronchitis, dyspnea, decreased appetite, weight loss and vomiting; most of them were gastrointestinal in nature [3, 4]. A higher percentage of patients in the nintedanib groups had myocardial infarction; the clinical significance of this finding is unknown, so they are requested further observations in larger cohorts [4]. Future nintedanib trials should focus on patients with pulmonary function tests more affected than mild to moderate; information on proper duration of treatment is also needed [8].

7. PIRFENIDONE

Pirfenidone is an oral antifibrotic drug with pleiotropic effects. It has been shown to regulate important profibrotic and proinflammatory cytokine cascade *in vitro* and to reduce fibroblast proliferation

and collagen synthesis in animal models of lung fibrosis [9]. Treatment with pirfenidone for 1 year in the most recent trials resulted in clinically meaningful reductions in disease progression in patients with IPF [11]. Patients from CAPACITY trial treated with high doses of pirfenidone (2403 mg/day) showed a reduction in FVC decline during the 72-week treatment period. Pirfenidone treatment in ASCEND trial increased 6-minute-walk distance, progression-free survival and improved dyspnea when comparing with placebo [11]; mortality and dyspnea scores did not differ. Patients from both trials reported more treatment-related adverse effects as nausea, dyspepsia, stomach discomfort, vomiting, anorexia, fatigue, photosensitivity, and rash compared with placebo [10], but gastrointestinal and skin-related adverse effects rarely led to discontinuation [11]. Pirfenidone is a very costly intervention and the decision-making process should be shared with the patients. Future research should focus on optimal duration of the treatment, effect on patients with more affected pulmonary functional tests, with emphysema or with coexisting airflow obstruction [10].

CONCLUSIONS

Derived from the trials results, there are some practical things to know: there is no particular phenotype where nintedanib was more or less active and no data are available on the efficacy and safety on nintedanib in patients with FVC less than 50% of predicted. It seems that nintedanib is an appropriate first-line therapy for patients with IPF; it is appropriate for patients who have failed to respond to pirfenidone therapy, but there is no clear answer when to choose nintedanib or pirfenidone as initial therapy [3]. Up to now there is no evidence to suggest a certain point after which nintedanib would not be efficacious anymore; still, in clinical cases with a proved disease progression under nintedanib, it should be considered a change in therapy if there is available a second drug [3].

ABBREVIATIONS

ALAT Latin American Thoracic Association.

ATS American Thoracic Society.

DLCO Diffusing capacity of the lung for carbon monoxide.

ERS European Respiratory Society.

IDL Interstitial lung disease.

IIP Interstitial pulmonary pneumonia.

IPF Idiopathic pulmonary fibrosis.

FEV1 Forced expiratory volume in one second.

FGF Fibroblast growth factor.

FVC Forced vital capacity.

HRCT High-resolution computed tomography.

JRC Japanese Respiratory Society.

PDGF Platelet-derived growth factor.

SGRQ St. George's Respiratory Questionnaire.

VEGF Vascular endothelial growth factor.

UIP Usual interstitial pneumonia.

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