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Definition, evaluation and therapy of progressive fibrosing interstitial lung disease associated with rheumatic diseases - a consensus paper of the Romanian Society of Rheumatology and Romanian Society of Pneumology

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ABSTRACT

Interstitial lung diseases (ILD), of which the most well-known is idiopathic pulmonary fibrosis (IPF), are a heterogeneous group of diseases, with similar, inflammatory and/or fibrosing mechanisms, which lead to the rapid decline of lung function and implicitly to a high degree of morbidity and mortality. Besides IPF, other interstitial lung diseases, such as those associated with connective tissue diseases, the most common being rheumatoid arthritis and systemic sclerosis, can develop a progressive fibrosing phenotype. Thus, because they have similar pathogenic mechanisms and clinical manifestations, all these diseases are described under the term of progressive fibrosing interstitial lung disease (PF-ILD). It is recommended that the diagnosis, clinical and paraclinical evaluation of ILD be made through a standardized management, within a multidisciplinary team that must include a pulmonologist, radiologist and rheumatologist, evaluation after which the subsequent treatment will be decided. Early diagnosis leads to an effective therapeutic intervention and decreased mortality. The progressive character has been defined if the progression occurs despite the current optimal management and treatment, which includes glucocorticoids and immunosuppressive therapy, at which point the indication of the antifibrotic treatment appears. The complete evaluation of ILD involves a rigorous anamnesis and clinical examination to identify environmental and professional risk factors, the patient's chronic medication, family and personal history, the onset of the disease, as well as the identification by auscultation of bilateral basal crackles. From the paraclinical examination, the most important is the imaging studies (standard chest X-rays and mandatory HR-CT) which provide information about the anatomy, pattern, evolution in time or clues related to the underlying disease. The progressive character has been defined if the progression occurs despite the current optimal management and treatment, which includes glucocorticoids and immunosuppressive therapy, at which point the indication of the antifibrotic treatment appears. Evaluation of lung function is very important to complete the patient picture with PF-ILD, and the gold standard is the combination of

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spirometry, body plethysmography with diffusing capacity for carbon monoxide (DLCO), gasometry and an exercise test. Using this information, the optimal treatment will be led by the same multidisciplinary team that established the diagnosis, taking into account many aspects related to the characteristics of the disease, the cause, the safety profile and it will be monitored according to the existing protocols.

Keywords: interstitial lung diseases, connective tissue diseases, early diagnosis, progressive character, optimal treatment

INTRODUCTION

Interstitial lung diseases (ILD) are a heterogeneous group of conditions that involve the lung parenchyma through inflammatory and/or fibrosing mechanisms. Some of them are associated with autoimmune disorders, especially connective tissue diseases, while others are associated with exposure to certain environmental factors, such as hypersensitivity pneumonitis, and others are of unknown cause. From the category of idiopathic interstitial lung diseases, the best known is idiopathic pulmonary fibrosis (IPF), which is at the same time the most severe form and represents by its definition the prototype of chronic fibrosing interstitial lung disease with progressive phenotype, characterized by the rapid decline of lung function. This group of ILD is well known for its high degree of mortality and morbidity [1,2].

Besides IPF, other forms of ILD, such as those associated with connective tissue diseases or hypersensitivity pneumonitis, may develop progressive fibrosing phenotypes. From the histological point of view, this phenotype is characterized by self-maintained fibrosis, which leads to the decline of lung function, the decrease in the quality of life of patients and to early mortality. Due to the fact that all these diseases, regardless of their cause, share similarities in terms of pathogenesis and clinical manifestations, radiological findings, lung function, and prognosis they are described by the general term of progressive fibrosing interstitial lung disease (PF-ILD) [3,4].

The diagnosis, clinical and paraclinical evaluation of ILD are recommended to be made through a standardized management, within a multidisciplinary team that must include a pulmonologist, rheumatologist, radiologist and a pathologist who will decide together the subsequent treatment [3,4].

As mentioned above, IPF has by its definition a progressive phenotype, and the antifibrotic treatment with nintedanib or pirfenidone has demonstrated in recent studies a positive effect on the evolution of the disease and prophylaxis of exacerbations. For many patients with PF-ILD there is so far no other treatment besides glucocorticoids and off-label immunosuppressants, with varying degrees of therapeutic success. Due to the similarities between IPF and PF-ILD, it was proposed that the efficacy and tolerability of antifibrotic therapy with nintedanib and pirfenidone should be also evaluated in PF-ILD. Thus, the purpose of several meetings of specialists in recent years, for example from Austria or France, was to establish a unanimously accepted consensus for patients with chronic fibrosing ILD of non-IPF progressive phenotype type to benefit from antifibrotic treatment, especially in those who highlight the appearance of honeycomb fibrosis or those with the form of extended disease. A secondary objective was that patients with fibrosing ILD who, following the multidisciplinary discussion, do not receive treatment or receive immunosuppressants, should be closely monitored to highlight possible progression [3,4].

DEFINITION

IPF is the prototype of PF-ILD and it is diagnosed especially in men over 60 years of age, smokers or with smoking history, characterized by rapid deterioration of lung function, thus having a reserved prognosis. Two types of antifibrotic drugs for IPF, nintedanib and pirfenidone have been approved. Taking this into account, it is obvious that the early diagnosis and treatment of PF-ILD are necessary [5-7].

PF-ILD share similar characteristics from a genetic, pathophysiological and clinical point of view, characterized by a progressive fibrotic process (Figure 1, Table 1). This category includes hypersensitivity pneumonitis (HP), sarcoidosis with progressive fibrosing interstitial pulmonary damage, connective tissue disease-associated interstitial lung disease (CTD-ILD) which, despite immunosuppressive treatment, can develop the progressive fibrosing phenotype with unfavorable prognosis [4,8-10]. One of the most common CTD-ILD is the one associated with systemic sclerosis, diagnosed in approximately 70-80% of cases. SLSI and SLSII studies have shown a favorable effect on pulmonary fibrosis of mycophenolate mofetil (MPM). Other therapeutic options in patients who were refractory to MPM are cyclophosphamide and biological agents such as tocilizumab and rituximab [11,12]. The 2019 SENSCIS study included 576 patients with systemic sclerosis with ILD and showed the effectiveness of nintedanib which reduced the decline in forced vital capacity, leading to approval by the European Medicines Agency of

the indication of nintedanib for this disease. In the same study it was shown that the smallest decline in lung function was found in patients who received MPM and nintedanib [13]. INBUILD is another important study that showed that treatment with nintedanib led to a reduction in lung function decline regardless of the pattern on high-resolution computed tomography (HRCT) of usual interstitial pneumonia (UIP) or non-UIP [14]. Several subgroups of patients were introduced in this study, and the effects of nintedanib were consistent in all subgroups, which led to the approval of its indication for PF-ILD in 2020.

It is very important to define these diseases, as well as to define a standardized management and a diagnosis as early as possible, in order to make the right therapeutic choice. The most common fibrosing interstitial pneumopathies are IPF, hypersensitivity pneumonitis, unclassifiable interstitial lung disease (uILD) and sarcoidosis, with an estimated prevalence of 50-70/ 100,000 inhabitants. In addition to IPF, which has by definition a progressive fibrosis character, it is estimated that the percentage of patients with fibrosing ILD who develop a progressive phenotype is up to 30% [8-10]. The progressive character has been defined if the progression occurs despite the current optimal management and treatment, which includes glucocorticoids and immunosuppressives, at which point antifibrotic treatment is indicated [8,10].

EVALUATION

History and clinical examination

Symptoms of PF-ILD patients occur when the evolution of the disease is already in an advanced stage. Often patients complain of exercise dyspnea and dry cough. In the case of CTD-ILD, specific symptoms should also be taken into account, such as joint pain, Raynaud's phenomena, muscle or skin involvement [5,8]. Medical history will identify professional or environmental factors (feathers,

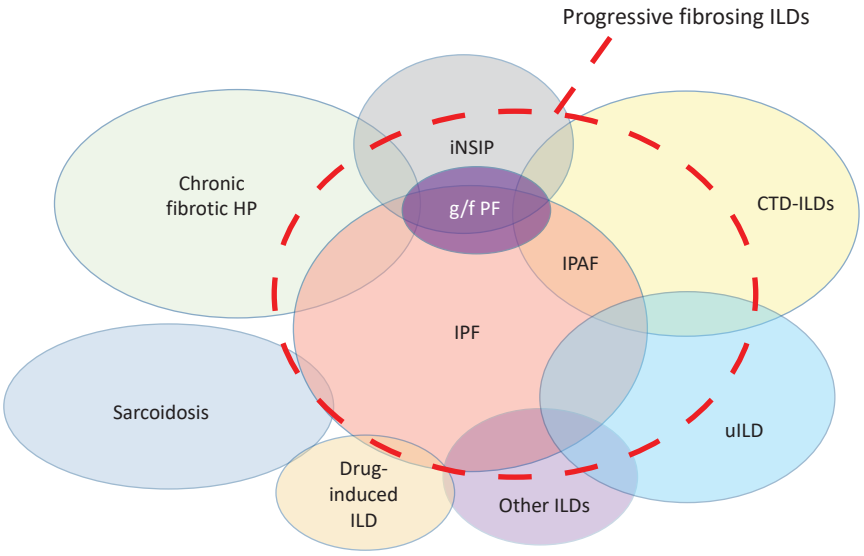

FIGURE 1. Schematic representation of ILD types associated with progressive fibrosis [15] Abbreviations: CTD – connective tissue disease; g/f PF - genetic and/or familial pulmonary fibrosis; HP - hypersensitivity pneumonitis; ILD – interstitial lung disease; IPAF: interstitial pneumonia with autoimmune features; IPF – idiopathic pulmonary fibrosis; NSIP - nonspecific interstitial pneumonia; uILD – unclassifiable ILD

TABLE 1. Types of ILD

inducing factors	disease	Examples
environmental factors	hypersensitivity pneumonitis	organic and inorganic inhaled agents: farmer's lungs, bird fancier's lung;
	pneumoconiosis	silicosis, asbestosis, coal pneumoconiosis;
	radiation-induced or drug-induced ILD	drugs (amiodarone, methotrexate) or external radiation;
	smoking-induced diseases	Langerhans cell lung histiocytosis, smoking-induced interstitial fibrosis;
	fibrosis stage of respiratory distress syndrome	infection (viral or bacterial pneumonia), poisoning, post-transfusion injury, fat embolism, pancreatitis, drug overdose;
	chemical pulmonary damage	toxic fumes and gases: chlorinated components, sulfur dioxide or nitrogen;
intrinsic factors	autoimmune disease	connective tissue diseases, inflammatory bowel disease, autoimmune hepatitis, primitive biliary cholangitis, vasculitis;
	familial pulmonary fibrosis	congenital dyskeratosis, Hermansky-Pudlak syndrome, type 1 Gaucher disease, type B Niemann-Pick disease;
unidentified factors	post-transplant syndromes	restrictive post-lung allograft syndrome, restrictive syndrome after hematopoietic stem cell transplantation.
	IPF NSIP sarcoidosis uILD	

Abbreviations: ILD – interstitial lung disease; IPF – idiopathic pulmonary fibrosis; NSIP - nonspecific interstitial pneumonia; uILD – unclassifiable interstitial lung disease.

organic compounds etc.), previous and current medication (amiodarone, chemotherapy etc.), smoking, family history, as well as the onset of the disease. From the point of view of clinical examination, auscultation is essential for the identification of bilateral basal crackles, since they are a predictive factor for the evolution of fibrosis [8,16].

Laboratory workup

Upon diagnosis, recommended blood tests include complete blood count, evaluation of liver and kidney function, evaluation of inflammatory syndrome (erythrocyte sedimentation rate, C-reactive protein), as well as tests to exclude heart damage (creatin-kinase, muscle-brain creatin-kinase, troponin, N-terminal pro-brain natriuretic peptide, myoglobin, aldolase) and immunological makers (rheumatoid factors, antinuclear antibodies, anti-citrullinated peptide antibodies, possibly extended antinuclear antibody panel, systemic sclerosis panel, myositis panel) [8,17,18]. If, following clinical and laboratory evaluation, a hypersensitivity pneumonitis is suspected, specific tests are recommended that consist of precipitin antibody reaction, which together with the clinical and imaging data, can lead to a certain diagnosis [19].

Imaging

Pulmonary or thoracic conventional X-rays are the first imaging investigation that will be performed in a patient suspected of lung fibrosis, but it cannot give a specific diagnosis, it can only guide the differential diagnosis (for example, cardiac disease) or it can give clues about the severity of the disease [20]. The diagnosis of ILD is based entirely on HRCT. It provides information about anatomy, imaging pattern, evolution over time or clues related to the underlying disease [21]. The patterns found on HRCT images in patients with PF-ILD are:

a) reticular pattern and/or "ground glass" opacities which may be accompanied by peripherally located traction bronchiectasis;

b) "honeycombing" lesions, found in 30-40% of patients [22];

c) UIP pattern, characterized by peripheral subpleural and basal reticulations, with "honeycombing" lesions and traction bronchiectasis;

d) NSIP pattern, characterized by "ground glass" opacities, consolidations and reticulations in basal areas, which may be accompanied by traction bronchiectasis [20,23].

In addition to an accurate diagnosis, HRCT can provide data on the prognosis of the disease: UIP with typical "honeycombing" lesions and traction bronchiectasis has an unfavorable prognosis, while the "ground glass" pattern in NSIP, associated with consolidations and reticulations, has a good response to immunosuppressive therapy [22,24,25].

However, HRCT imaging data will always be corroborated with the medical history and the clinical and laboratory data, as well as with those obtained after the evaluation of lung function, in order to establish the diagnosis, the optimal treatment and the prognosis. Complex software based on artificial intelligence algorithms can quantitatively evaluate fibrotic lesions, but such technology is not available at this time in current medical practice, especially because of prohibitive prices [20,26].

Lung function tests

Very important in the complete evaluation of patients with PF-ILD is the evaluation of lung function, and the gold standard is represented by the combination of spirometry, body-plethysmography and diffusing capacity of the lungs for carbon monoxide (DLCO), arterial blood analysis (ABG) and an exercise test. The most important functional parameters are forced vital capacity (FVC) and DLCO [10,17,27]. ABG or pulse oximetry must be performed both at rest and during exercise, this providing data on oxygen requirements and can reveal early changes in diffusion [2,5,28]. The most used exercise test is the 6-minute walking test (6MWT), which is performed according to a standardized protocol [10,29].

Bronchoscopy, broncho-alveolar lavage (BAL) and lung biopsy

Invasive methods such as bronchoscopy, BAL and lung biopsy are necessary if all the above clinical, laboratory and functional investigations did not establish the diagnosis. BAL is used especially if an inflammatory pathology is suspected and can help establish the diagnosis, since it can allow a differential cell count of nucleated immune cells which can guide the positive and the differential diagnosis [30]. For example, a high number of neutrophils raise the suspicion of an infection, while moderately high values of neutrophils and eosinophils are found in IPF [17,18].

Lung biopsy can be performed endoscopically (cryobiopsy) or by classical transbronchial surgery. Taking into account the fact that it involves surgery that carries certain risks, the decision of its necessity must be taken within the multidisciplinary team, where its benefits and risks will be balanced in a given clinical situation [8,17]. There is a possibility that the radiological pattern does not coincide with the histological pattern, the latter being able to identify several patterns. It goes without saying that the histological sample will be examined by an experienced pathologist in a specialized center.

The multidisciplinary board

The multidisciplinary board includes pulmonologists, radiologists, rheumatologists and pathologists and has the responsibility of diagnosis and treatment. This team has already become a standard in numerous clinics [1,17,18]. It has already been demonstrated that debating the case of a patient with IPF within a multidisciplinary board increases the accuracy of the diagnosis and has prognostic relevance [17,31,32]. In recent years, due to the fact that new therapeutic options have appeared, attention for CTD-ILD has significantly increased, therefore the relationship between pulmonologists and rheumatologists has a special importance [8,10,33].

Disease progression evaluation

The progression of the disease is very important in the complete evaluation of the patient with PF-ILD. Following routine investigations, risk factors for the evolution of ILD can be identified. A common example in current practice is the appearance of "honeycombing" UIP on HRCT imaging in a patient with rheumatoid arthritis which is an unfavorable prognostic factor [34,35]. At the moment there is no clear recommendation regarding the parameters that can estimate the progression of PF-ILD. An example used in various clinical trials is shown in Table 2. In terms of IPF, FVC is a longitudinal parameter that can be correlated with survival rate and has been selected as the primary endpoint in clinical trials with antifibrotic therapy [7,27]. Also, in IPF, DLCO is correlated with mortality and is used both in clinical trials and in current practice [27]. It is recommended to intercorrelate these parameters and to correlate them with the 6MWT, in order to decrease the degree of variability [10]. Another important part of the discussion is related to the time interval until PF-ILD diagnosis. It is known that in clinical trials, patients with PF-ILD in the placebo group had a decline in lung function similar to that of patients with IPF in the placebo group, even though the average age of the former was lower. This suggests that most likely the time frame in which the patient is monitored for the establishment of antifibrotic therapy could be shorter and that when signs of progression appear, this therapy would bring important benefits [9]. Another problem is related to the choice of FVC as the main marker of progression, especially in patients with emphysema, a situation in which an increased value of FVC can be misleading [9,36,37]. Therefore, it was proposed to take into account other risk factors of progression, such as the presence of "honeycombing" lesions or the extension of fibrotic lesions on HRCT with more than 20%, factors correlated with increased mortality [9,38]. Thus, even when a clear radiological progression cannot be highlighted, in patients who have progression risk factors, the immediate initiation of antifibrotic therapy should be considered in the case of patients with IPF or, possibly, a combination with immunosuppressive therapy in CTD-ILD [9].

PF-ILD MANAGEMENT

The most important objective in the management of PF-ILD is to stabilize or slow the progression of fibrosis. The therapeutic objective in PF-ILD is to improve symptoms, to limit the functional degradation of the lungs and to improve the quality of life. Although PF-ILD is a progressive incurable chronic disease, in addition to drug treatment, palliative therapy will always be added. It includes improvement of individual symptoms through psychological or psychotherapeutic counseling and rehabilitation. If until this moment it was important to discuss in a multidisciplinary board of specialists, this is the moment when it is important to communicate effectively between the doctor and the patient and possibly the family, in order to establish the common objectives and expectations, as well as the benefits and risks of the drug treatment [33].

TABLE 2. Proposed criteria for progression evaluation [12]

study	phenotype	Criteria
INBUILD (nintedanib) [14]	non-IPF, PF-ILD	in the last 24 months despite the optimal management: relative decline of FVC by ≥ 10%; relative decline of FVC by ≥ 5% and worsening of symptoms or fibrosis progression on HRCT; worsening of symptoms or fibrosis progression on HRCT.
Maher et al. (pirfenidone) [39]	uILD	in the last 6 months despite therapy: absolute decline of FVC by ≥ 5%; worsening of symptoms in the absence of other causes (e.g., heart).
RELIEF (pirfenidone) [40]	PF-ILD, CTD-ILD, fibrotic NSIP, asbestos-associated ILD, HP	despite adequate therapy: absolute decline of FVC by ≥ 5%/year over at least 6-24 months with at least 3 measurements.
George et al. ("position paper") [10]	PF-ILD definition	in the last 24 months: relative decline of FVC by ≥ 10%; relative decline of FVC by ≥ 5% and decline of DLCO by ≥ 15% or fibrosis progression on HRCT or worsening of symptoms; worsening of symptoms and fibrosis progression on HRCT.

Abbreviations: CTD-ILD – connective tissue disease-associated interstitial lung disease; DLCO – diffusing capacity of the lungs for carbon monoxide; FVC – forced vital capacity; IPF – idiopathic pulmonary fibrosis; HP – hypersensitivity pneumonitis; HRCT – high resolution computed tomography; NSIP – nonspecific interstitial pneumonitis; PF-ILD – progressive fibrotic interstitial lung disease; uILD – unclassifiable interstitial lung disease.

The multidisciplinary board has the responsibility to establish and identify patients who present after the investigations a typical fibrotic character as in IPF or if there are active inflammatory signs. Also, the individual evaluation of the risk-benefit ratio will be carried out by the multidisciplinary board involving the patient and subsequently the treatment will be initiated. In general, when making treatment decisions, it is recommended to take into account the following aspects (Table 3):

a) Not all cases of PF-ILD, with the exception of IPF, require immediate treatment. It is recommended that in patients who have a slow evolution, with mild symptoms or in elderly patients with comorbidities, a careful monitoring strategy should by applied, instead of potentially hazardous drug therapy.

b) Current data available in the specialized literature should be taken into account, such as the recent extension of therapeutic indications for nintedanib in PF-ILD [14]. It is recommended in cases of UIP to carefully monitor and immediately initiate antifibrotic treatment in case of proof of progression. These recommendations are especially valid for patients whose extent of lung damage is more than 20% of lung volume since diagnosis or for patients with "honeycombing" lesions on HRCT [9].

c) If the association with an autoimmune disease is suspected or known, it is recommended to consult the rheumatologist for the evaluation and establishment of background therapy. In the evolution of the disease, if the progression of fibrosis is observed, the opportunity of adding antifibrotic treatment to the immunosuppressive medication or its replacement with antifibrotic therapy will be evaluated, depending on the respiratory functional parameters and the safety profile.

d) In cases of HP, the primary objective is to identify and eliminate antigens. Subsequently, depending on the extension of the pulmonary "ground glass" damage, it will be decided to initiate immunosuppressive therapy. If progression of fibrotic lesions is observed, antifibrotic therapy should be added.

TABLE 3. ILD treatment

inducing factors	phenotype	Management
environmental factors	HP	glucocorticoids, azathioprine, MPM, leflunomide, cyclophosphamide, rituximab, pirfenidone, nintedanib
	pneumoconiosis	nintedanib
	radiation or drug-induced ILD	glucocorticoids, cyclophosphamide, MPM, infliximab, nintedanib
	smoking-associated ILD	cladribin, nintedanib
	fibrosis stage of respiratory distress syndrome	glucocorticoids, nintedanib
	chemical pulmonary damage	glucocorticoids, nintedanib
intrinsic factors	autoimmune disease	- idiopathic inflammatory myositis: glucocorticoids, methotrexate, azathioprine, MPM, cyclophosphamide, cyclosporine, tacrolimus, rituximab, nintedanib [10] - systemic lupus erythematosus: glucocorticoids, methotrexate, azathioprine, MPM, cyclophosphamide, rituximab, belimumab, nintedanib [33] - systemic sclerosis: glucocorticoids, azathioprine, MPM, cyclophosphamide, rituximab, tocilizumab, nintedanib [11,12,15] - Sjogren's syndrome: glucocorticoids, azathioprine, MPM, cyclophosphamide, rituximab, nintedanib [41] - rheumatoid arthritis: glucocorticoids, methotrexate, azathioprine, cyclophosphamide, leflunomide, rituximab, nintedanib [14]
	familial ILD	nintedanib, pirfenidone
	post-transplant syndrome	pirfenidone, nintedanib, montelukast [42]
unidentified factors	IPF	pirfenidone, nintedanib
	NSIP	glucocorticoids, azathioprine, MPM, rituximab, cyclophosphamide, nintedanib [39]
	sarcoidosis	glucocorticoids, methotrexate, azathioprine, hydroxychloroquine, leflunomide, cyclophosphamide, MPM, rituximab, infliximab, adalimumab, nintedanib [16,40]
	uILD	pirfenidone, nintedanib [20].

Abbreviations: HP – hypersensitivity pneumonitis; ILD – interstitial lung disease; IPF – idiopathic pulmonary fibrosis; MPM – mycophenolate mofetil, NSIP – nonspecific interstitial pneumonitis, uILD – unclassifiable interstitial lung disease.

e) In the case of uILD or idiopathic NSIP, the standardized evaluation will be carried out within the multidisciplinary board who will establish whether immunosuppressive therapy is justified or whether the immunosuppressive and antifibrotic therapy will be associated.

f) It is recommended to evaluate the therapeutic response no later than 3-6 months after treatment initiation. Depending on this, the subsequent therapeutic conduct will be decided. It is recommended that the evaluation be done in specialized ILD centers.

g) In deciding to initiate immunosuppressive therapy in patients with PF-ILD, it should be noted that scientific evidence for efficacy is limited and the safety profile is questionable (for example, increased risk of infections).

h) Current available data indicate that associating immunosuppressive treatment (especially MPM and methotrexate) with antifibrotic treatment (nintedanib) is safe [14,39]. There are certain subgroups of patients who may benefit from this association. In order to avoid possible side effects, these drugs should not be initiated simultaneously, but sequentially.

Finally, non-pharmacological treatment (elimination or avoidance of antigens in the case of HP, oxygen therapy, smoking cession, pulmonary rehabilitation) must be constantly associated with drug therapy. In the case of patients with unfavorable prognosis, it is recommended to discuss the possibility of lung transplantation and possibly to establish a first contact with such a specialized center. It is recommended to observe the vaccination scheme: pneumococcal vaccine, influenza, pertussis, SARS-CoV-2 [43].

CONCLUSION

ILD are a group of diseases which, regardless of their cause, lead to the decline of lung function, to the decrease of the patients' quality of life and implicitly to increased morbidity and mortality. It is very important that the diagnosis be established as early as possible, based on clinical and paraclinical information, especially through HR-CT, within a multidisciplinary team which will include specialists in pulmonology, rheumatology and imaging. In addition to establishing the diagnosis, the progression of the disease will also be evaluated through criteria that have been proposed in several studies. Also, the optimal treatment will be led by the same multidisciplinary team that established the diagnosis, taking into account many aspects related to the characteristics of the disease, the cause, the safety profile and it will be monitored according to the existing protocols.

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