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Review

A review on Interstitial Lung Diseases: an overview from diagnosis to innovative therapies

Revisione sulle Interstiziopatie Polmonari: una panoramica dalla diagnosi alle terapie innovative

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ABSTRACT

Interstitial Lung Diseases (ILDs) enclose a wide heterogeneous group of more than 200 pathological disorders, which are characterized by an inflammatory and/or fibrotic pattern in the respiratory tract. In recent years, significant developments in the understanding of their pathogenesis have led to considerable progress in the therapeutic field and in improving clinical outcomes. COVID-19 pandemic has also had an important impact on the course of interstitial disease, particularly that which developed following infection in both symptomatic and asymptomatic patients, as well as in patients with pre-existing interstitial disease prior to infection. The purpose of this review is to describe clinical, radiological and therapeutic features of some of the most common interstitial lung diseases, as well as the multidisciplinary diagnostic procedure that underlies an increasingly accurate diagnosis.

Le Interstiziopatie Polmonari (ILD) racchiudono un ampio gruppo eterogeneo di oltre 200 disturbi patologici, caratterizzati da un quadro infiammatorio e/o fibrotico a carico delle vie respiratorie. Negli ultimi anni, gli importanti sviluppi nella comprensione della loro patogenesi hanno portato a notevoli progressi in campo terapeutico ed al miglioramento degli esiti clinici. La pandemia COVID-19 ha avuto un impatto importante anche sul decorso della malattia interstiziale, in particolare quella sviluppatasi in seguito all'infezione sia in pazienti sintomatici che asintomatici, nonché in pazienti con malattia interstiziale pre-esistente all'infezione. Lo scopo di questa revisione è quello di descrivere le caratteristiche cliniche, radiologiche e terapeutiche di alcune delle più comuni interstiziopatie polmonari, nonché l'iter diagnostico multidisciplinare alla base di una diagnosi sempre più accurata.

INTRODUCTION

The term Interstitial Lung Disease (ILD) represents a multitude of pathologies, many, but not all of which primarily affect the pulmonary interstitium. ILD is characterized by inflammation or fibrosis in the interstitial space, which primarily leads to impaired gas exchange, leading to dyspnea and, in many cases, respiratory failure to death.

To date, it is estimated that more than 200 pathological disorders can give rise to ILD.

The most common form of ILD is Idiopathic Pulmonary Fibrosis (IPF), which is characterized by a worse prognosis, with an average life expectancy for patients without treatment of approximately 3-5 years after diagnosis. In contrast, other ILDs, particularly those characterized by a mainly inflammatory pattern, such as non-fibrotic hypersensitivity pneumonitis and several sarcoidosis, have a better clinical course and usually respond better to treatment.

Over the past decade, there have been significant developments in understanding the pathogenesis of many ILDs, leading to considerable progress in the therapeutic field as well as in improving clinical outcome. These therapeutic developments have in turn led to a change in the characterization and treatment of some ILDs, which have the ability to cause progressive pulmonary fibrosis.[1]

ILD can originate as: i) idiopathic, ii) autoimmune, iii) secondary or from known causes: related to environmental and/or occupational exposure, iatrogenic, linked to rheumatological diseases, iv) granulomatous.

Pathogenesis

Several mechanisms underlie the pathogenesis of the development of Fibrotic ILD (PF-ILD). Typically, the process is triggered by repeated inflammatory injury to the epithelium or vascular damage, causing not only cellular injury but also affecting the repair system. Consequently, this causes the migration of fibroblasts from the lung epithelium and peripheral circulation to the site of injury and their activation into myofibroblasts. This leads to the secretion of a rigid extracellular matrix with dysfunctional alveolar tissue. In addition, pro-fibrotic mediators are released by macrophages and lymphocytes in combination with increased stiffness of the alveolar tissue. Subsequent fibroblastic activations trigger a continuous cycle of progressive pulmonary fibrosis.[2]

Pro-fibrotic mediators such as Platelet-Derived Growth Factor (PDGF), Tumor Necrosis Factor-α (TNF-α), Transforming Growth Factor-β (TGF-β) and Matrix Metalloproteinase (MMP) are assumed to contribute to the pathogenesis process.[3]

The pathogenesis in 65% of patients remains unknown. However, evidence of the involvement of exogenous factors is increasing in several conditions. Sarcoidosis, for example, is attributed to a combination of individual predisposition and exposure to a still unknown agent. High exposure to metals and wood dusts, on the other hand, have been identified as risk factors for IPF.

Exogenous causes are identified in 35% of patients with ILD, especially organic substances (causing extrinsic allergic alveolitis, *i.e.* hypersensitivity pneumonitis), inorganic substances (causing pneumoconiosis), drugs (some antibiotics such as nitrofurantoin, antiarrhythmic drugs such as amiodarone, chemotherapeutic drugs such as cyclophosphamide) and infections.

Autoimmune and connective tissue diseases such as lupus, polymyositis and rheumatoid arthritis are also predisposing to the development of the disease, as are hepatitis C and Human Immunodeficiency Virus (HIV) infections and the presence of familiarity for ILDs.

Smoking and aging are also risk factors for the development of interstitial disease.

Symptoms most commonly seen at onset include dyspnea, coughing and fatigue. Some individuals may be asymptomatic for several months or a few years before diagnosis. On physical examination, common is the finding of detached velcro crackles, a characteristic noise of this disease that is auscultated by the clinician.[4]

The clinical course and quality of life of people with ILD is affected by a multitude of intrapulmonary or extrapulmonary comorbidities; these include pulmonary hypertension, Chronic Obstructive Pulmonary Disease (COPD), lung cancer, Gastro-Oesophageal Reflux Disease (GERD), obstructive sleep apnea syndrome and cardiovascular disease.[5]

Diagnosis

Chest X-ray and axial Computed Tomography (CT) show a typical appearance of nodular infiltrates and fine reticulations, while in more advanced stages fibrotic distortion and sometimes the aspect of a 'honeycombing' lung appears.

The diagnosis and classification of ILDs has been revolutionized by High-Resolution Computed chest Tomography (HRCT), which in many cases prevent to patient further invasive diagnostic procedures.

The American Thoracic Society/European Respiratory Society has provided the criteria for defining the UIP pattern that is characteristic of interstitial lung disease and is the hallmark of IPF. Distinctive signs on HRCT radiological investigation for interstitial pneumonia include lung volume loss, bronchiectasis and traction bronchiolectasis, honeycombing, possible presence of concomitant ground-glass opacities and fine reticulations. The typical distribution of the Usual Interstitial Pneumonia (UIP) pattern is subpleural with basal predominance.

Additional diagnostic patterns found by HRCT include Probable UIP pattern, indeterminate UIP pattern and non-UIP pattern.[6]

Probable UIP pattern is characterized by the presence of subpleural reticulations with basal predominance, as is observed in the UIP pattern, without honeycombing. However, the presence of ground-glass opacities is also possible.

Indeterminate UIP pattern, on the other hand, presents ground-glass opacity and limited subpleural reticulation, with no evident fibrous features.

Finally, a non-UIP pattern is defined when there is a suspicion of IPF in some cases of fibrotic lung disease. This HRCT pattern is suggestive of an alternative diagnosis; examples include the presence of bronchocentric fibrosis in superior lung lobes and mosaic attenuation pattern typical of Hypersensitivity Pneumonitis (HP), fibrotic post-hilar retraction in sarcoidosis or ground-glass opacity with no subpleural involvement in Non-Specific Interstitial Pneumonia (NSIP).[7]

Pulmonary function tests and Pulmonary Diffusing Capacity of Carbon Monoxide (DLCO), show a "restrictive" and, less frequently, "obstructive" ventilatory defect; in addition, hypoxemia is present, especially during effort. The diagnosis is often made using a combination of clinical, pathophysiological, immunological and radiological findings. A careful history is the first step in identifying the presence of ILD; this is because domestic or occupational exposure to organic antigens, pneumotoxic drugs or dusts known to induce pneumoconiosis (including asbestos, silica or coal dust) are all possible external causes of the development of ILD.[8]

In the course of investigations during the detection of new ILD with suspected IPF, serological tests may be required to exclude connective tissue disease. If, on radiological investigation with HRCT, a probable UIP pattern is found, cellular analysis of their fluid with Bronchoalveolar Lavage (BAL) technique may also be requested. For an accurate diagnosis in individuals for whom clinical, radiological and bronchoscopic information is insufficient to provide confirmation of a specific diagnosis, histopathological evaluation may be required.[9]

Surgical lung biopsy is performed by Video-Assisted Thoracoscopy (VATS) and is the gold standard for the histopathological detection of interstitial pathology. Alternatively, a transbronchial cryobiopsy can be performed; this method of investigation is less invasive than surgical biopsy, with a lower incidence of complications but a similar level of diagnostic accuracy when the case under investigation is discussed in a multidisciplinary setting. A further alternative to these methods is lung cryobiopsy.[10]

Despite the multitude of diseases that represent ILD, some have a higher incidence in the population. Of these, the most common and widespread form is pulmonary fibrosis, followed by other less frequent interstitial diseases such as sarcoidosis, Organizing Pneumonia (OP), pneumoconiosis and hypersensitivity pneumonitis. An accurate classification of pulmonary interstitial diseases requires an integrated approach between pulmonology, pathology and radiology, which is the gold standard for better diagnostic accuracy.

Interstitial Lung Disease classification

Idiopathic Pulmonary Fibrosis (IPF)

IPF represents the most common form of idiopathic interstitial disease and is considered a rare chronic disease of unknown etiology, leading to a progressive and irreversible loss of lung function due to the development of fibrosis. It manifests itself through symptoms such as cough and dyspnea, impairing the patient's quality of life.

Lung transplantation is limited to a minority of cases and patients are initially treated with antifibrotic therapy, as they do not respond to immunosuppressive therapy, together with additional supportive therapy.[9]

Despite recent advances, current therapies slow disease progression and the prognosis remains poor compared to other interstitial diseases, with a median survival of 2-3 years for untreated subjects.

The pathogenesis underlying the development of IPF is complex and poorly understood, but involves abnormal healing following repeated injury to the alveolar system. This leads to uncontrolled proliferation, differentiation and activation of fibroblasts, which in turn drives the expansion of the cellular matrix with loss of normal lung architecture. As a result, inflammation appears to play a dominant role in the pathogenesis of the disease.

The average age at diagnosis of IPF is between 65 and 70 years, with the incidence increasing with age. The number of diagnoses worldwide is increasing; this is attributable to several causes, including an aging population and a better understanding of the disease due to improved diagnostic tools.

Risk factors for IPF include male sex, smoking, inhalation of metal or wood dust and genetic factors.

Non-Specific Interstitial Pneumonia (NSIP)

NSIP is considered a distinct entity among Idiopathic Interstitial Pneumonias (IIP), This pattern however occurs not only as an idiopathic condition, but also in a variety of settings including HP and drug toxicity, as well as in some patients with familial pulmonary fibrosis. The radiological feature on HRCT most commonly observed in NSIP is bilateral ground-glass opacities. In addition, irregular reticular opacities with traction bronchietcasis and bronchiectasies occur in about 75% of cases. The absence of subpleural involvement may be helpful in discriminating NSIP from UIP.[11]

Sarcoidosis

A multisystem disease of unknown etiology, characterized by the infiltration of various organs by non-necrotizing granulomas, in which environmental factors and genetic susceptibility participate in the formation process. The disease occurs regardless of the ethnicity and age, although individuals of African American and Scandinavian ethnicity have a higher incidence than the Caucasian population.

The disease generally occurs in individuals under 50 years; approximately 70% of cases occur between the ages of 25 and 40, with a second peak incidence in women over 50.

Sarcoidosis can follow two different courses: a time-limited course, in which two-thirds of patients evolve towards remission of the disease within 12-36 months and a chronic course, which requires prolonged treatment for 10-30% of patients.

Symptoms are mostly non-specific and may include disorder of concentration, fever, weight loss and night sweats; respiratory symptoms include cough, dyspnea and chest pain.

Systemic treatments are intended for patients with organ involvement and life-threatening conditions.[12]

Organizing Pneumonia (OP)

A syndrome that develops following lung damage, caused by an inflammatory reaction to alveolar connective tissue damage. It can be secondary to infection, drug toxicity, connective tissue disease, inhalation of substances of abuse, organ transplantation or radiotherapy, but in some cases it can be idiopathic.

The clinical course of patients with OP is non-specific and subacute, with a pattern of malaise, cough and dyspnea, which may persist for several weeks.

According to recent studies, the prevalence of this disease is higher than expected.

Therefore, although OP is considered almost a diagnosis of exclusion, the increased incidence and prevalence should include patients with an abnormal chest pattern on X-ray, who have not improved after antimicrobial therapy.[13]

Pneumoconiosis

This is a predominantly occupational disease, caused by the inhalation of mineral dust, which leads to lung dysfunction. The dusts are mainly inorganic particles, such as free silica dust, asbestos fibers, coal mine dust and mixed silicate dust. Pneumoconiosis is characterized by a picture of chronic lung inflammation associated with fibrosis.

It is a worldwide disease with a high incidence in recent years and still remains a serious global public health problem due to the lack of dust prevention in the workplace, the lack of diagnosis at early stages and the limited treatments available for the disease.[14]

Hypersensitivity Pneumonitis (HP)

This is a complex syndrome resulting from repeated exposure to a wide range of potential antigens, which is characterized by a granulomatous inflammatory pattern. In more than half of the cases, the sensitizing antigen cannot be identified.

Non-fibrotic form is mediated by formation of immune complexes, whereas fibrotic form occurs through alveolar and dendritic cells presenting antigens to T-lymphocytes.[15]

Interstitial Lung Diseases associated with autoimmune diseases

A small proportion of ILDs is associated with autoimmune diseases. The most common of these include rheumatoid arthritis, systemic lupus erythematosus, progressive systemic sclerosis and dermatomyositis.

Interstitial lung disease is the most common manifestation found in rheumatoid arthritis, which can affect up to 60% of patients who present this systemic disease. It is usually detected by HRCT investigation and is one of the main causes of disease and death in rheumatoid arthritis.[16] Although rheumatoid arthritis is more common in female subjects, the association of Rheumatoid Arthritis-Related Interstitial Lung Disease (RA-ILD) is more frequently found in male subjects.[17]

There are also genetic studies that have identified gene variants associated with an increased risk of developing pulmonary fibrosis, in a pattern that shows similarities between RA-ILD and familial IPF. Among these, the MUC5B variant, which is the major genetic risk factor for IPF, has also been shown to be associated with RA-ILD, particularly ILDs presenting UIP

patterns and hypersensitivity pneumonitis.[18] These similarities in the mechanisms found in RA-ILD and interstitial lung disease with UIP patterns suggest possible shared pathways in the pathogenesis and mechanisms of fibrosis development, which could lead to the development of therapeutic strategies that would benefit both diseases.[19]

In systemic sclerosis, an autoimmune connective tissue disease that affects the skin tissue as well as characterized by a dysregulation of the immune system with progressive fibrosis, interstitial lung disease is the most common cause of death; a mortality rate of up to 30% is estimated in subjects with systemic sclerosis[20], and may be as high as 40% at 10 years. Standard therapy in the treatment of these patients is based on a combination of immunosuppressive agents, such as mycophenolate and cyclophosphamide, together with antifibrotic therapy and/or biological therapy.[21]

Inflammatory myopathies include a number of diseases such as polymyositis and dermatomyositis, autoimmune diseases characterized by muscle involvement and extramuscular manifestations. The association of myositis with ILDs is associated with increased mortality. ILD is associated in 40% of cases[22] with more severe extramuscular involvement, which is tightly correlated with reduced quality of life and a worse prognosis. This is more pronounced in patients with an acute/subacute form of ILD than in patients with a chronic form. Standard therapy is based on the use of glucocorticoids with immunosuppressants.[23]

Although rheumatoid arthritis, systemic sclerosis and autoimmune dermatomyositis are the most common autoimmune diseases associated with ILDs, there are other diseases, such as Sjogren's Syndrome (SjS), mixed connective tissue disease and systemic lupus erythematosus, that can be associated with ILDs.[24]

In individuals with SjS, the most frequently encountered pattern of pulmonary interstitial disease is Non-Specific Interstitial Pneumonia (NSIP), present in 30-40% of patients.[25]

In Mixed Connective Tissue Disease (MCTD), a disease characterized by a pattern combining systemic lupus erythematosus, systemic sclerosis and polymyositis, the association with ILD is accompanied by a poor prognosis. The most common pattern in 50-80% of these patients is characteristic of NSIP In a number of studies conducted in cohorts of patients with MCTD, ILD is associated with increased mortality and the extent of reticulation at HRCT, together with the absence of arthritis and anti-Ro antibodies are associated with progression.[26]

ILDs are less frequent in Systemic Lupus Erythematosus (SLE), occurring in only 2-4% of cases.[27] Again, the most common radiological pattern found in these patients is NSIP, which occurs in 40-55% of subjects with SLE, while the UIP pattern appears in 9-30% of cases.[28]

Unclassifiable Interstitial Lung Diseases

There are also patients with ILDs for whom a specific diagnosis cannot be defined; for this reason, such ILDs are defined as unclassifiable or indeterminate. They are characterized by the absence of a specific diagnosis following multidisciplinary discussion and review of available clinical, radiological and pathological data. The threshold for defining an ILD as unclassifiable has been applied inconsistently over the years and not clearly defined. However, the International Working Group has recently suggested that the classification of unclassifiable ILD should be defined as the absence of a principal diagnosis considered most likely not to be.[29] It is estimated in the literature that about 12% of all ILDs is defined as unclassifiable.[30]

Unclassifiable ILDs thus falls into a heterogeneous and poorly defined category and this definition could be used as justification to refrain from looking for additional underlying causes.

Drug-related Interstitial Lung Diseases

The development of interstitial lung disease can also occur following the use of therapies, particularly antineoplastic ones. This occurs in approximately 23-51% of cases and most commonly following therapy with bleomycin, everolimus, erlotinib, trastuzumab-deruxtecan and immune checkpoint inhibitors.

Drug-Induced Interstitial Lung Disease (DIILD) is defined as a recognized subtype of ILDs resulting from exposure to drugs that cause inflammation accompanied by interstitial fibrosis, according to the American Thoracic Society/European Respiratory Society (ATS/ERS) classification. Clinical, pathological and radiological features are rarely specific and difficult to discriminate from other interstitial pneumonias. Moreover, the clinical phenotype, imaging and histopathological patterns differ significantly between drugs and between patients taking the same drug. For this reason, DIILD is therefore a diagnosis of exclusion.[31]

In patients diagnosed with cancer, DIILD is mainly associated with the use of cytotoxic chemotherapy, target therapy and immunotherapy. The diagnosis and treatment of this subset of ILDs requires a multidisciplinary approach to ensure a better patient outcome.

Additional drugs related to the development of ILDs include anti-rheumatic drugs, amiodarone and antibiotics.

The risk of developing ILDs increases when these drugs are used in combination and may also be dose-dependent.[32]

Treatment of interstitial pathology

Various pharmacological treatments are used in the management of interstitial pathology, which include: i) non-steroidal anti-inflammatory drugs; ii) steroidal anti-inflammatory drugs or corticosteroids; iii) antifibrotic agents; iv) immunosuppressants; v) antibiotics; vi) oxygen therapy.

The evolution towards new therapies

IPF has long been devoid of viable therapeutic options; only in the last decade have two oral antifibrotic therapies, pirfenidone and nintedanib, been developed, which have shown efficacy in improving Forced Vital Capacity (FVC) over one year in IPF patients with moderate pulmonary dysfunction.

Although IPF is the most common form of ILD with progressive pulmonary fibrosis, there are other distinct types of ILDs that share a similar phenotype: Idiopathic Unspecified Interstitial Pneumonia (iNSIP), HP, Connective Tissue Disease-Associated ILD (CTD), Unclassifiable ILD (uILD) and sarcoidosis.

These diseases, when characterized by a progressive phenotype, are defined ILD with PF-ILD. They overlap with IPF, as they often share similar radiological, histopathological and clinical features.[2]

Nintedanib

Nintedanib, an oral intracellular tyrosine kinase inhibitor, acts against several receptors for tyrosine kinases, including PDGF, Vascular Endothelial Growth Factor (VEGF) and Fibroblast Growth Factor (FGF), leading to the disruption of the signaling pathway of fibroblast activation and proliferation.

The use of nintedanib has been extensively studied in the treatment of IPF, starting with the phase II TOMORROW study in 2011, continuing with the phase III INPULSIS study in 2014 and the INSTAGE/INJOURNEY studies in 2018. The results from the TOMORROW study showed that taking the 150mg dose of nintedanib twice daily improves FVC and consequently quality of life, and also reduces flare-ups in such patients. Data from the INPULSIS study also demonstrated an improvement in forced vital capacity.[33] The most commonly reported adverse event when taking nintedanib is diarrhea. As a result of these results nintedanib was approved for the treatment of patients with IPF and was included in the guidelines for the treatment of this condition.

The use of nintedanib was also investigated in the treatment of patients with interstitial disease other than IPF in the SENSCIS and INBUILD trials. In the first trial, the use in patients with systemic sclerosis related to ILD was evaluated, obtaining results comparable to previous trials in terms of improvement of FVC.[34] In the INBUILD trial, on the other hand, the use of the drug on patients with different PF-ILD was evaluated; again, the results were similar to previous studies.[35] This led to the approval of the use of nintedanib also in patients with Systemic Sclerosis-related ILD (SSc-ILD) in 2019 and subsequently also in patients with PF-ILD.

Pirfenidone

Pirfenidone is an oral drug with anti-inflammatory, anti-fibrotic and antioxidant properties. It acts mainly on fibroblast proliferation and on proteins and cytokines related to the fibrotic process, such as TGF-β and TNF-α.

The use of pirfenidone in patients with IPF has been evaluated in several randomized trials, starting with the CAPACITY I and II trials in 2011, continuing with the ASCEND trial in 2014 and RECAP in 2017. As early as the CAPACITY I trial, an improvement in FVC was demonstrated in patients treated with pirfenidone compared to placebo.[36] Pirfenidone was also associated, following the results of the ASCEND trial, with improved disease-free survival and, as a result, was approved by the FDA for the treatment of IPF.

As with nintedanib, trials have been conducted to evaluate its use in patients with PF-ILD. Among these, the LOTUS trial evaluated the use of the drug on patients with SSc-ILD;[37] the double-blind RELIEF trial evaluated the efficacy of the drug on patients with CTC-ILD, Chronic Hypersensitivity Pneumonitis (cHP), iNSIP and fibrotic disease related to asbestos exposure. These trials suggested that in cHP-ILD patients with disease progression despite the use of conventional therapy, pirfenidone was able to attenuate further FVC reduction and disease progression (Figure 1).[38]

Interstitial Lung Diseases (ILDs)	Antifibrotic Therapies	Recommendations
Interstitial Pulmonary Fibrosis (IPF)	Nintedanib Pirfenidone	UIP and UIP Probable patterns
Non-specific Interstitial Pneumonia (NSIP)	Nintedanib	At least one among: • Decline of FCV ≥10%; • Radiological progression disease; • Clinical decline (progressive pulmonary healing, dyspnoea and respiratory failure)
Sarcoidosis		
Organizing Pneumoniae (OP)		
Pneumoconiosis		
Hypersensitivity Pneumonitis (HP)		
Autoimmune-ILDs: • *Rheumatoid Arthritis-related ILD (RA-ILD)* • *Systemic Sclerosis related to ILD (Ssc-ILD)* • *Myositis related to ILD* • *Sjogren's syndrome related to ILD* • *Mixed Connective Tissue disease related to ILD* • *Systemic Lupus Erythematous related to ILD*		
Unclassifiable ILD		

Figure 1. Agenzia Italiana del Farmaco (AIFA) - approved antifibrotic therapies.

Interstitial Lung Disease and Covid-19

Covid-19 pandemic that started in 2020 had a strong impact on patients with respiratory diseases. The disruption of healthcare caused by the pandemic resulted in many changes in patients with ILDs.[39]

During the pandemic it became evident that patients with Covid-19 infection can develop typical expressions of an IPF pattern, which in many cases persists for a long time even after the infection has ended. Indeed, Covid-19 infection induces fibrotic changes that can alter biological mechanisms in the lungs, leading to stiffening of the tissue, with a pattern similar to pulmonary fibrosis.

Evidence of an association between viral infection and the development of pulmonary fibrosis in these patients emerged early during the pandemic, with the level of alteration from a state of fibrosis in OP to diffuse fibrotic disease following severe lung injury.[40] Furthermore, in a descriptive study conducted in Wuhan, radiological features in patients who died for Covid-19 infection were found to show fibrosis with bilateral ground-glass opacities; this radiological feature was found both in patients who had been symptomatic during infection and in asymptomatic patients.[41]

There are many factors that impact the course of Covid-19 post-infection lung fibrosis, causing its progression and life limitation. Among these, genetics is likely to play a key role.

On the other hand, pre-existing conditions of ILD and pulmonary fibrosis are associated with a risk of Covid-19 infection manifesting in a severe form.[42]

CONCLUSIONS

ILDs represent an increasing burden on the healthcare system and many of these diseases remain under the definition of orphan diseases. Much information regarding pathogenesis, clinical aspects and genetics still remains unknown for many ILDs. For this reason, further large-scale studies are needed. Pharmacological therapy remains unsatisfactory for most ILDs, even though considerable progress has been made in recent years through clinical studies conducted, particularly with regard to IPF.

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