Interstitial Lung Diseases

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1. Background

Interstitial lung diseases (ILD) are a heterogeneous group of pulmonary disorders characterized by varying degrees of inflammation and fibrosis resulting in the loss of alveolar function and impairment of gas exchange [1]. Idiopathic pulmonary fibrosis (IPF) is an entity that is included in the group of interstitial lung diseases of unknown etiology, being a severe form of pulmonary fibrosis that is associated with high morbidity and mortality [1][2][3].

IPF has a variable incidence depending on the population under study. Thus, in the United Kingdom, IPF has an incidence of around 7.44 cases per 100,000 inhabitants, while in the United States some series show an incidence of 16.3 cases per 100,000 inhabitants or even 93.7 cases per 100,000 people as described in a systematic review conducted by Hutchinson [4] covering the decade from 2001 to 2011. Overall, it is estimated that the worldwide prevalence may be close to 60 cases per 100,000 inhabitants. This entity predominantly affects males over 65 years of age [2][3][4].

Since its appearance, the coronavirus disease 2019 (COVID-19) pandemic has affected millions of people worldwide causing more than three million deaths. The available data indicate that a significant percentage of individuals suffering from severe acute respiratory syndrome caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) develop acute lung injury/acute respiratory distress syndromes (ALI/ARDS), which can become severe. Pulmonary fibrosis is a recognized sequel of ARDS. Currently, there is evidence of fibrotic changes in radiographic images of patients recovered from COVID-19 [5][6][7].

Although IPF is the most widely studied and most common fibrosing ILD, there are also other progressive fibrosing (PF)-ILDs such as certain connective tissue disease-associated ILDs, which evolve towards pulmonary fibrosis and present a similar behavior to IPF, characterized by worsening of respiratory symptoms, decline in lung function and early mortality despite standard of care treatment [1][2][3]. In the same line, the PROGRESS study showed data on patients with other chronic PF-ILDs who were admitted to a hospital in Lyon, France, between 2010 and 2017. This study showed that those patients who had a loss of a quarter of their lung function or a loss of forced vital capacity (FVC) ≥ 10%, had 3 year survival rates of 83% and 5 year survival rates of 72%. In addition, some factors were

shown to be associated with worse evolution, such as age > 70 years; FVC < 70% and/or diffusing capacity of the lungs for carbon monoxide (DLCO) < 40% at diagnosis; reduction in FVC ≥ 10% from the estimated value or decrease in DLCO ≥ 15% from the estimated value within 6–12 months of follow-up; and decrease > 50 m in the 6 min walking test at 6 months [8].

Indeed, much of the information given in this review is applicable to both IPF and other non-IPF ILDs with a fibrosing phenotype [1][2].

Regarding the pathophysiology of IPF and of other PF-ILDs, it is multifactorial and results in a progressive deterioration of lung function. Some risk factors for progression have been described, including environmental factors, microbial agents or some previous pathologies such as gastroesophageal reflux, which have a probable genetic basis that confers the patient a certain susceptibility to the disease [9].

IPF is the most common idiopathic interstitial pneumonia in the world. It is characterized by a heterogeneous, irreversible, progressive and unpredictable course associated with significant morbidity and poor prognosis after diagnosis [1][2][3]. There is growing evidence supporting that the disease originates from the interaction between the variable expression of genetic polymorphisms, changes related to cellular aging and exposure to certain environmental factors, such as smoking, industrial powders, chronic gastric microaspiration, viral infections and possibly alterations in the lung microbiome [1][3]. The lesions produced by repetitive exposures aberrantly activate the alveolar epithelial cells of genetically susceptible individuals, promoting apoptosis of the epithelium, recruitment of mesenchymal cells and increased vascular permeability. Unregulated epithelial/mesenchymal interaction results in the secretion of a variety of profibrotic cytokines, metalloproteinases and procoagulant mediators, which promote uncontrolled migration and proliferation, and differentiation in fibroblasts to myofibroblasts as well as fibrosis in the extracellular matrix. The main pro-inflammatory cytokines involved in fibrosis are tumour necrosis factor (TNF)-α and interleukin (IL)-1, as well as some fibrous factors such as transforming growth factor (TGF)-β and platelet-derived growth factor (PDGF) [1][2][3][4][5].

Patients present a nonspecific symptomatology, which is the fundamental cause of the delay in diagnosis. Accordingly, in order to reach a definitive diagnosis, it is essential to combine a detailed medical history with the realization of radiological imaging studies and sometimes with histopathological studies obtained through a pulmonary biopsy (PB). Currently, the gold standard for diagnosis of IPF and other non-IPF PF-ILDs is multidisciplinary discussions that can improve the precision of diagnosis, avoiding unnecessary tests such as pulmonary biopsy and optimizing patient management. The multidisciplinary team should include a pulmonologist, a radiologist, a pathologist, a thoracic surgeon, a rheumatologist and a specialist nurse [10].

Patients with IPF present with dyspnea, cough and asthenia, which are symptoms that cause a reduction in daily physical activity and muscle strength leading to a precarious quality of life and often result in social isolation with increased levels of dependence and immobility as the disease progresses and causing a significant number of cardiopulmonary complications. In addition, these patients experience depressive and anxiety disorders, creating a situation that is difficult to manage for both patients and their caregivers [11].

Another cause for the delay in the diagnosis of IPF is that this is an entity that can be easily confused with other respiratory pathologies requiring multidisciplinary assessment by the pulmonology, radiology and pathological anatomy services, thereby using more healthcare resources [10][12].

Lung transplantation is the only therapeutic option that appears to increase the life expectancy of patients with IPF. This procedure would be indicated when there is a higher probability of accelerated decrease in FVC and, therefore, a poor prognosis in the short term. As the knowledge of IPF has deepened and several technical advances have been achieved, especially in the area of transplant immunology and surgical procedures (involving both means and technique), the average age of recipients undergoing lung transplantation has increased in recent decades from 45 to 55 years. However, this therapeutic option has been extended in recent years to patients up to 65 years of age in specialized centers. Nevertheless, despite these advances, pulmonary recipients with IPF have an overall survival rate upon single transplantation between 4 and 5.5 years, depending on the series, and may exceed 10 years for bilateral pulmonary transplantation [10][11][12].

Traditionally, IPF treatment was based on immunosuppressants, glucocorticoids, oxygen therapy and palliative measures. However, the PANTHER-IPF study showed that treatment with azathioprine, N-acetyl cysteine and prednisone was associated with increased hospitalizations and mortality [13]. Currently, there are two drugs approved for this pathology that have been shown to delay lung deterioration associated with the disease with satisfactory safety and tolerability profiles. These two drugs are nintedanib and pirfenidone [14][15]. However, there is little information on the pharmacological interactions of these two agents in IPF patients who are usually polymedicated.

The group of COVID-19 patients most affected by severe disease present clinical characteristics highly similar to patients suffering from PF-ILD, rendering PF-ILD management more important than ever [5][6][7].

2. COVID-19 and ILD

SARS-CoV (Severe Acute Respiratory Syndrome Coronavirus) and MERS-CoV (Middle East Respiratory Syndrome Coronavirus) are genetically similar to SARS-CoV-2 and cause lung syndromes similar to COVID-19. At the end of the SARS pandemic on June 2003, 8422 people were affected and 916 died. On the other hand, MERS, which began in April 2012, infected 2519 recognized subjects out of which 866 died. Tomographic abnormalities in SARS included the following: rapidly progressive ground-glass opacities, some of them with consolidation of some regions of the lung; and apparent reticular changes approximately two weeks after the onset of symptoms, which persisted in half of the patients for about 4 weeks. A 15 year follow-up study of 71 patients with SARS showed that interstitial and functional abnormalities progressively decreased, resulting in recovery after the first 2 years following infection and then remained stable; at 15 years, only one patient had obstructive pulmonary disease and none had restrictive respiratory dysfunction, while 4–6% showed interstitial abnormalities [6]. Similar to the findings in SARS, ILD with a fibrosing phenotype has been reported in MERS [7].

Several cases of patients with severe pneumonia of unknown cause appeared in Hubei province, China, in December 2019. Almost one month later, these cases were reported to the World Health Organization (WHO). They started an outbreak that was later declared a pandemic by WHO. The causative agent of this disease was identified as a betacoronavirus RNA, similar to SARS-CoV, which was thus called SARS-CoV-2. This coronavirus causes lung, gastrointestinal and neurological disease. It has a diameter between 60 and 140 nanometers and is covered by an envelope formed by different spicules, which gives it a solar corona appearance. By genetic recombination, coronaviruses acquire the capacity to infect any host, including bats and humans. SARS-CoV-2 is able to infect the nasal and bronchial epithelia, as well as pneumocytes, through the binding of the spike (S) protein of viral spicules to its receptor on the cell surface, which is the angiotensin-converting enzyme-2 (ACE-2); this interaction triggers an inflammatory response and, subsequently, the clinical picture of pneumonia and/or respiratory failure [1][6]. In one of the first studies conducted in China during the pandemic, the characteristics of 1099 patients were reported. Out of these, 173 cases were severe, with an average age of 49 years; 57% were male; 28% were smokers; and 23.7% (over 70 years) presented comorbidities such as diabetes, hypertension and chronic obstructive pulmonary disease (COPD); 5% of the cases were in intensive care; 2.3% on mechanical ventilation; and 1.4% of patients died [16]. As of June 2021, 180,569,000 infections and 3,912,200 deaths have been reported worldwide [17].

Fibrotic changes have been found in chest computerized tomography (CT) in patients with COVID-19. Available data indicate that one-third of the recovered patients develop fibrotic abnormalities, 47% have impaired DLCO and 25% have decreased total lung capacity. In a study by Huang et al., all patients who survived had varying degrees of fibrotic damage ranging from subtle linear opacities to diffuse distribution of crazy paving pattern, with extensive fibrosis evidenced in 52% of patients. In another study by Zhou et al. including 62 patients, 21 (33.9%) had fibrotic changes, which were more likely to occur in advanced stages of the disease (8 to 14 days from onset of symptoms) than in earlier stages (less than 7 days). Similarly, Pan et al. reported fibrotic changes in chest CT in 11 out of 63 patients during acute illness. These reshapings are supported by autopsy reports. Early fibrotic changes in the course of the disease suggest repair attempts following lung damage; all this results in pulmonary sequelae, which include impaired exercise capacity, fibrotic lung tissue and impaired diffusing capacity. However, although pulmonary function can be improved over time, moderate fibrosis could be irreversible in some patients [18][19]. Thus, it would make sense to apply the same strategy as in other non-IPF PF-ILDs in these patients and antifibrotic agents could play a relevant role.

The early identification of subpopulations of patients developing PF-ILD phenotype after COVID-19 infection is important since it is presumed that, by acting early in the course of ARDS, the development of lung damage could be avoided, delayed or decreased [18]. Several markers associated with mortality risk including age, disease severity, time of Intensive Care Unit (ICU) stay, mechanical ventilation and hyperinflammatory markers may be potential predictors of PF-ILD. Other factors such as male sex, smoking and underlying diseases have also been described. In addition, prolonged fever prior to hospital admission, tachypnea and eosinopenia at admission may be useful as a combination of early risk indicators [19].

Age: Pulmonary fibrosis is most often reported in elderly individuals. The exact reason for this association is unknown; however, older individuals are more susceptible to SARS, MERS and SARS-CoV-2 and are more likely to possess severe symptoms [17].

Disease severity: According to the WHO, 80% of COVID-19 cases are mild, 14% develop severe symptoms and 6% are very severe. Comorbidities such as high blood pressure, diabetes and coronary artery disease are factors associated with increased severity. Laboratory findings that correlate with increased severity are as follows: lymphocytopenia, leukocytosis and lactate dehydrogenase (LDH) increase. Serum LDH levels have been used as a marker of disease severity following acute lung damage. LDH is an indicator of lung tissue destruction and correlates with mortality risk. Peak LDH levels were significantly correlated with the risk of pulmonary fibrosis after infection in MERS and SARS [17]. In a meta-analysis, Chen et al. reported that elevated LDH values were associated with a 12-fold increase in the risk for severe COVID-19 and concluded that LDH levels can be used to predict severe disease [20].

Time of hospitalization at the ICU and mechanical ventilation: Five percent to twelve percent of COVID-19 patients required ICU admission. Although disease severity is closely related to the time of hospitalization at the ICU, mechanical ventilation provides an additional risk of ventilator-induced lung damage. Ventilator-associated lung damage is an acute damage that is initiated or exacerbated by mechanical ventilation and is associated with increased mortality in ARDS. Pressure and volume abnormalities induce this damage, resulting in the release of proinflammatory modulators, worsening of acute lung damage, increased mortality and pulmonary fibrosis in survivors. In a follow-up study of 27 patients with ARDS who received mechanical ventilation, 23 (87%) had pulmonary fibrosis between 110 and 267 days after extubation [17].

Smoking: It is associated with chronic oxidative stress, increased expression of inflammatory cytokines and pulmonary fibrosis. The harm associated with smoking continues even after smoking cessation. A systematic review by Vardavas and Nikitara showed that smokers are 1.4 times more likely to have more severe symptoms of COVID-19 and 2.4 times more likely to need the ICU, mechanical ventilation or die than non-smokers [17].

Chronic Alcoholism: Alcohol abuse is associated with recurrent pneumonia due to the aspiration of gastric contents. Clinical and experimental studies show that alcoholism causes glutathione depletion, chronic oxidative stress, inflammation and induction of TGF-B in the lungs, thereby increasing the risk of acute lung injury and pulmonary fibrosis [17].

Patients should be advised not to leave the house and to use non-face-to-face methods for consultations (telemedicine), to obtain medicine stocks (they can be formulated for 3 months) and, if required, to ask for help in order to avoid leaving the house (from family or friends). They should also take into account the different recommendations on fever, odynophagia, dry cough and dyspnoea for 1 week and consult for suspected COVID-19. A management strategy should be established with patients and family members, if possible, with recommendations on how to proceed during a mild exacerbation at home, including indications about warning signs for them to attend emergencies or to contact their physician and reminding them that they may not

necessarily be infected with COVID-19. Medications for interstitial lung disease should be maintained at the dose recommended by the attending physician but should be discontinued at the time of acute COVID-19 infection in order to avoid drug interaction or side effects. The patient's immune response appears to play an important role in the pathophysiology of both acute lung injury and ARDS. Patients with COVID-19, particularly those with pneumonia and ARDS have elevated levels of proinflammatory cytokines and other inflammatory biomarkers. Currently, the most commonly used drugs for the acute phase of COVID-19 are glucocorticoids. In fact, in the RECOVERY trial, dexamethasone has shown a moderate but significant reduction in mortality among those patients who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support. However, despite this clinical trial being one of the most robust studies regarding the use of glucocorticoids in COVID-19, its methodology is somehow questionable among other reasons because no severity markers were recorded. Furthermore, several routes of administration of dexamethasone, oral or intravenous, were used [21]. Notwithstanding the need of further evidence, glucocorticoids seem to be the cornerstone of the treatment of the acute phase of COVID-19 to date. Additionally, the combination of supportive therapy along with antiviral treatment, oxygen therapy and anticoagulation must be emphasized [22]. In order to clarify the role of anti-inflammatory and immunomodulatory treatment of the acute phases of COVID-19 on the occurrence of long-COVID and post-ARDS interstitial lung disease, further research is needed. Finally, pulmonary rehabilitation in the acute and inflammatory phases is essential for the full recovery of lung function in these patients.

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