

The Spectrum of Progressive Fibrosing Interstitial Lung Disease: Clinical and Managed Care Considerations

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Progressive fibrosing interstitial lung diseases (ILDs) comprise a diverse group of diseases. Although causes are not always known, some causes have been identified, including underlying conditions such as a connective tissue disease (CTD); exposure to organic antigens, such as feathers; or environmental toxins, such as asbestos. Some cases have no known cause, notably idiopathic pulmonary fibrosis (IPF).¹⁻³

In progressive fibrosing ILDs, patients with various initial ILDs and etiologies develop a common chronic fibrosing pathological pathway.⁴ The overall economic impact of progressive fibrosing ILDs cannot be simply assessed by analyzing the cost of that common fibrosing pathway. This article explores the characteristics of the various diagnostic categories that contribute to the progressive fibrosing ILD phenotype and highlights key variables in the discussion of the economic and managed care implications of progressive fibrosing ILDs.

Progressive Fibrosing ILDs: An Overview

Historically, IPF has garnered much of the research interest of ILD specialists. However, under the umbrella term *pulmonary fibrosis*, the non-IPF group of diseases represents a much larger segment of the ILD population.⁵ Common features among ILDs with a progressive fibrosis phenotype suggest the possibility for a common treatment pathway, although it is recognized that treatment success may vary according to the disease entity.¹ In addition, the common genetic variants that underlie the progressive phenotype of IPF are present in patients with progressive fibrosing ILDs.¹ Certain individuals with progressive fibrosing ILDs in these ILD disease groupings who are historically thought to be at lower risk for progression and mortality can actually progress with an IPF-like disease course and experience significant morbidity and mortality in the span of a few months to years.^{1,6} Thus, failing to recognize patients at high risk for progressive fibrosing ILDs early in their disease course may contribute substantially to the overall financial impact of these diseases.

This wide array of conditions can be condensed into major groupings of disease: collagen vascular diseases (CVDs), occupational

ABSTRACT

Progressive fibrosing interstitial lung diseases (ILDs) encompass a wide range of diseases, including hypersensitivity pneumonitis, occupational diseases, granulomatous diseases, drug-induced diseases, and idiopathic pneumonitis. Given the vast number of progressive fibrosing ILDs and the disparities in clinical patterns and disease features, understanding their clinical and economic impact presents significant challenges. Historically, treatment options for progressive fibrosing ILDs include anti-inflammatory drugs and immunosuppressive. The lack of effective options and guideline recommendations, however, has rendered treatment difficult. In March 2020, nintedanib was approved by the FDA for the treatment of patients with chronic fibrosing ILDs with a progressive phenotype, becoming the first therapeutic agent to receive an indication for this set of diseases. The approval was based on data from the phase 3 randomized, double-blind, placebo-controlled, parallel-group INBUILD trial. Questions regarding the cost of medications, their effects on disease and comorbidities, patient selection, and combination strategies remain to be answered.

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disorders, chronic hypersensitivity pneumonitis, sarcoidosis and other granulomatous lung diseases, drug-induced pneumonitis, and idiopathic interstitial pneumonias. The idiopathic interstitial pneumonias encompass disorders that include IPF, idiopathic pleuroparenchymal fibroelastosis, idiopathic nonspecific interstitial pneumonitis (NSIP), unclassifiable pulmonary fibrosis, and familial pulmonary fibrosis. Although these idiopathic disorders may be radiographically distinct from IPF, they often share similar clinical features.¹ The term *unclassifiable interstitial pneumonia* was introduced into international guidelines in 2013 to designate those idiopathic interstitial pneumonias that cannot be categorized based on clinical, radiological, or histopathological findings, or in the absence of biopsy results.⁷ A diagnosis of either idiopathic NSIP or unclassifiable idiopathic interstitial pneumonia has implications for the patient's prognosis and selection of a treatment course, although both conditions have some similarities to IPF. (See the article on page S111 of this scientific supplement for further information on this topic.)

“Historically, the selection of an appropriate treatment for progressive fibrosing ILDs has been challenging because of the absence of effective treatment options and a lack of guideline recommendations.”

The first section of this review focuses on CVDs. The diagnosis and treatment of connective tissue diseases are inherently complex, particularly because of pulmonary complications that may occur in patients affected by these conditions. In this respect, CVD-associated ILD (CVD-ILD) can serve as a model for other ILDs with a progressing phenotype beyond IPF, as the proper treatment of this family of diseases helps to demonstrate why multidisciplinary teams are often consulted to make a diagnosis and create a therapy plan^{1,8}—and why the economic burden to the system and the psychological toll on patients are so severe.⁹

CVD-Associated ILD

CVD describes a heterogeneous family of autoimmune disorders—including rheumatoid arthritis (RA), systemic lupus erythematosus,

systemic sclerosis (SSc), polymyositis/dermatomyositis (PM/DM), and antineutrophil cytoplasmic antibody-associated vasculitis—that may be associated with fibrotic ILD.¹⁰ Presence of ILD in CVD negatively affects prognosis; in one cohort study among patients with RA with ILD, median survival was 3 years, and the 5-year survival rate was 38.8%.¹¹ Epidemiologic evidence on the prevalence and incidence of CVD-ILD is limited. It is believed that rates of CVD-ILD are higher in women and in patients aged younger than 50 years.¹

ILD has been recognized to occur in most of the CVDs.¹ In some cases, fibrotic ILD can be the initial manifestation of a CVD. The inflammatory myopathies (eg, PM/DM) are particularly notorious for this, resulting in rapidly progressive fibrosing ILD with significant morbidity and mortality, within months of diagnosis in some cases.¹² Findings suggest that among patients with fibrotic SSc-ILD, a forced vital capacity (FVC) below 70% in the first 4 years of diagnosis impacts survival, particularly in those patients who showed an annual rate of FVC decline minimum of approximately 5%.¹³ The lung is a common site of tissue injury in the majority of autoimmune diseases, but a true understanding of prevalence and incidence is complicated by the use of differing diagnostic methods in published studies.¹⁴

Overall, the pathology of ILD in CVD is dominated by inflammation and fibrosis, with radiologic and histopathologic patterns including NSIP and usual interstitial pneumonia (UIP).¹⁵ NSIP is associated with a more favorable prognosis compared with UIP, although there is a distinct variability in prognosis depending on the underlying disease. In a study among patients with scleroderma lung disease, the 5-year survival rates were 90% and 82% for NSIP and UIP patterns, respectively,¹⁶ whereas in results from another study of RA-associated ILD, the UIP pattern conferred a poor prognosis, with 50% mortality at 5 years.¹⁷

Determining the etiology of CVD-ILD can be challenging, often requiring close collaboration of a multidisciplinary team. One study indicated that patients who were referred to a specialty center for ILD with the concern of IPF had their diagnosis changed almost 30% of the time to CVD-ILD after evaluation by a multidisciplinary team of ILD specialists, thoracic radiologists, pathologists, and rheumatologists. Even when CVD-ILD was correctly identified, the diagnosis was changed to an alternate CVD-ILD 36% of the time, and these changes in diagnosis resulted in changes in treatment in 80% of those patients.¹⁸

It is difficult to estimate the cost of care of CVD-ILD. A large meta-analysis of 8 studies, including all forms of treatment for RA, found that the per-patient annual total cost of care ranged from \$3266 to \$25,260. Analyses of studies in which patients were treated only with biologic disease-modifying antirheumatic drugs found that per-patient annual cost of care ranged from \$26,469 to \$52,837; analyses of studies in which patients received only biologic medications found the mean annual per-patient total cost of care

to be \$36,053.¹⁹ However, the only study that specifically examined the economic impact of RA-ILD found that approximately 72% of patients had at least 1 all-cause inpatient admission each year, and the mean 5-year cost of care was \$173,405.²⁰ Only 38.5% of patients were still alive at the end of 5 years.

Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis is a diffuse, complicated ILD initiated from repeated exposure to an antigen, most commonly of an avian, microbial, or chemical nature.^{1,21} Genetic susceptibility and/or environmental variables may be predisposing risk factors prior to antigen exposure.²² The incidence and prevalence of hypersensitivity pneumonitis are largely unknown; reported rates differ globally, and estimates are further confounded by the fact that hypersensitivity pneumonitis is often misdiagnosed.^{22,23}

Chronic hypersensitivity pneumonitis shares many features with IPF, so it is often difficult to differentiate between them.²¹ The pathology of hypersensitivity pneumonitis, similar to that of IPF, is characterized by alveolar epithelial injury with concurrent abnormal repair mechanisms that potentiate fibroblast expansion and activation, excessive collagen deposition, and destruction of the lung architecture. Radiographic features of hypersensitivity pneumonitis tend to overlap with those of IPF, and diagnosis is often dependent on determining a causative antigen, determining the temporal relationship between exposure and disease, and identifying mosaic attenuation on chest imaging and poorly arranged non-necrotizing granulomas on pathology.¹

Perhaps not surprisingly, then, survival rates in patients with progressive hypersensitivity pneumonitis with either a UIP or NSIP pattern are similar to those of patients with IPF.²² In a cohort of 142 patients with a diagnosis of hypersensitivity pneumonitis, median survival was 5 years, and presence of lung fibrosis predicted shorter survival (4.9 years vs 16.9 years), whereas identification of the inciting antigen predicted longer survival (median, 18.2 years, vs 9.3 years in individuals with an unknown inciting antigen; $P < .01$).²⁴ There are also genetic similarities between IPF and chronic hypersensitivity pneumonitis that may have impacts on survival, with telomere lengths less than 10% associated with the reduced survival seen in IPF.²⁵

The optimal management of chronic hypersensitivity pneumonitis remains unknown. Historically, patients with a progressive fibrosing phenotype have been treated with therapeutic agents commonly used for CVD-ILD, without the benefit of randomized controlled clinical trials. In an uncontrolled retrospective analysis, patients who received a combination regimen of prednisone, azathioprine, and acetylcysteine had worsened survival compared with those who did not receive therapy, a finding that echoed earlier results from the PANTHER-IPF study.^{26,27} Mycophenolate and prednisone may be good options for treatment of subacute,

inflammatory subtypes but have not been rigorously studied in progressive fibrosing phenotypes.²⁷

The economic impact of chronic hypersensitivity pneumonitis is difficult to determine, due to a lack of evidence. Population-based registries reported that hypersensitivity pneumonitis accounted for 1.5% to 12.0% of incidental cases of ILD during the 1990s, but a higher prevalence may be seen in regions of the United States with higher rates of agricultural enterprise.²⁸ Antigen avoidance is the most important treatment for this disorder, but identification of the offending antigen can be challenging due to lack of specificity in testing.²⁹

Avoidance may not simply mean changing jobs or removing a beloved parrot from the home. Mitigation of water damage leading to mold infestation may be hidden from view and require an expensive construction project to repair. Many people in the agricultural industry own their farming operations, and ensuring antigen avoidance in these situations may entail economic loss. Despite the initial costs associated with the avoidance of environmental antigens, slowing disease progression may result in long-term economic benefit with the preservation of quality health years. The current health care and insurance systems are not structured to address potential financial impacts of necessary mitigation to operationalize antigen avoidance.

Occupational Diseases

A subset of ILD cases occur as a result of occupational exposures—specifically caused by inhalation of noxious inorganic dusts, which are retained in the lungs.¹ The US prevalence rates of asbestosis and silicosis are unknown and rates vary globally. The disease impact is unclear, owing to numerous confounding variables, such as issues related to accessing health care resources among individuals employed in skilled labor.¹³ Other identified sources of exposure include farming, livestock, metal dust, coal, sand, and dust from preparing dental prosthetics.¹

Patterns of disease seen on high-resolution CT (HRCT) may mimic other forms of ILD. In the case of advanced silicosis, the progressive fibrosis pattern in the lungs' upper lobes may be similar to findings in patients with sarcoidosis with pulmonary fibrosis, although some patients with silicosis may present with a UIP pattern. On the other hand, HRCT findings in patients with fibrosing asbestosis are similar to those of patients with IPF, although the presence of pleural plaques provides a distinguishing diagnostic indicator.¹

In patients with either silicosis or asbestosis, the extent of exposure does not appear to correlate with increased risk of mortality, suggesting that even small amounts of exposure could be consequential. In a review of 354 claimants for compensation for pulmonary asbestosis, the total estimated exposure to asbestos did not predict survival, but it did predict the degree of disability and the extent of radiographic profusion; the latter, in turn, was a risk factor for increased mortality.² Within the cohort, pneumoconiosis, bronchitis

and emphysema, tuberculosis, respiratory cancer, and malignant pleural mesothelioma all contributed to excess mortality.²

Granulomatous Diseases

Granulomatous disorders are a family of disease entities composed of infections, vasculitis, immunological upsets, leukocyte oxidase defect, and neoplasia, all sharing the common histological feature of granuloma formation.³⁰ A granuloma is defined by an aggregation of inflammatory cells, activated macrophages, Langerhans giant cells, and lymphocytes.³¹ The pathologic pathway to granuloma formation is multifactorial and complex, with a number of host and environmental factors interacting to mediate and drive fibrosis.³⁰ The fibrotic process in granulomatous diseases is driven by accumulation of fibroblasts and extracellular matrix around the granuloma. Notably, the patterns of fibrosis differ among granulomatous diseases.³²

One of the most widely studied granulomatous disorders is sarcoidosis. The prevalence of sarcoidosis is estimated to be 242 cases per million adults, with higher rates among females vs males and among Black vs White patients.³³ From 2010 to 2013, the median annual cost of care for patients with sarcoidosis was \$18,663, but the mean was more than \$32,000; for patients in the top 5% seen over the 4-year study period, the total cost of care was more than \$240 million, and the mean cost per patient in the top 5% per year was \$93,201.³⁴

Fibrotic lung disease develops in about 20% of individuals with sarcoidosis, according to results of one study.³⁵ Nonresolving inflammation in pulmonary sarcoidosis is a significant risk factor for development of pulmonary fibrosis.³⁶

Drug-Induced Diseases

A number of drugs have the potential to induce respiratory diseases such as ILD.³⁷ For example, pulmonary toxicity has been observed in patients who use the antiarrhythmic drug amiodarone.³⁸ The clinical manifestation of amiodarone pulmonary toxicity is heterogenous, with 5% to 7% of patients developing pulmonary fibrosis; this, in turn, is associated with a poor prognosis if not diagnosed early.³⁸ Pulmonary toxicity from nitrofurantoin is also observed, particularly in individuals on chronic suppressive therapies for urinary tract infections or those with preexisting ILD.³⁹

Several chemotherapy agents have also been linked to pulmonary complications.⁴⁰ For example, in the phase 2 DESTINY-Breast01 clinical trial, which evaluated trastuzumab deruxtecan in patients with pretreated HER2-positive metastatic breast cancer, ILD was found in 13.6% of patients, including 4 patients with ILD of grade 5.⁴¹ This requires further investigation and requirements of monitoring and managing these pulmonary symptoms.⁴¹ The clinical presentation and radiographic appearance of drug-induced ILD are highly variable and nonspecific, and no established criteria exist for making

a diagnosis.⁴⁰ The prevalence of drug-induced ILD is unknown, as good reporting mechanisms do not exist due to limitations related to *International Classification of Diseases* codes as well as underdiagnosis.³⁷ Treatment options for these conditions are limited by a number of factors, including the variable pattern of injury. Furthermore, ceasing use of the therapeutic agent may be required, thus complicating the care of the patient for their primary condition.

Idiopathic Pneumonitis Beyond IPF

Pneumonitis with a progressive fibrosing phenotype that is distinguishable from IPF, but still of uncertain etiology, is rare. The category of idiopathic pneumonitis beyond IPF includes desquamative interstitial pneumonitis, first described in 1965,⁴² and the more recently described entity called idiopathic pleuroparenchymal fibroelastosis.⁴³ Idiopathic pneumonitis also includes members of the family of diffuse lung diseases that affect full-term infants who are influenced by mutations in their genes that encode for surfactant proteins B and C and ABCA3.^{44,45}

Pleuroparenchymal fibroelastosis is a rare ILD characterized by dense fibrosis of the visceral pleura and subadjacent lung parenchyma. Pleuroparenchymal fibroelastosis has been associated with a range of potential causes, such as treatment exposure and organ transplant, although no direct links have been identified.^{43,46} Management strategies are limited. Supportive measures such as supplemental oxygen are frequently required, and lung transplantation should be considered in advanced cases.⁴³ Prognosis, while variable, is generally poor; one study suggested that advanced-stage pleuroparenchymal fibroelastosis portends a more dire prognosis than IPF.⁴⁷

Desquamative interstitial pneumonia is recognized as an idiopathic interstitial pneumonia related to cigarette smoking.⁴² When this condition was first described, the discovery of large cells within the alveolar spaces were suspected to be desquamated epithelial cells, but these were later found to be macrophages.^{42,48} Patients with desquamative interstitial pneumonia often present with nonspecific symptoms, including dyspnea and cough with or without sputum production.⁴⁸ Experts generally agree that cessation of exposure (ie, stopping tobacco use or removing sources of occupation exposure) is a necessary first step of treatment. The role of cytotoxic and immunosuppressive agents is unknown.⁴⁸

Disease Impact and Implications

The large number of ILDs with a progressive fibrosis phenotype, the array of potential clinical patterns associated with each disease, and the disparity in disease features and prognosis across the spectrum of these diseases create enormous complexity for managing patients. Accurate diagnosis and treatment are urgently needed, as mortality is much higher in patients with progressive fibrosing ILD than in those without progressive disease.⁸ Acute exacerbations

often require hospitalization, and the in-hospital mortality rate may be as high as 50%.⁸

Comorbidities in non-IPF ILD with a progressing fibrosis phenotype have a substantial impact on the patient's quality of life; they also add to the economic burden of institutions and the health care system.⁸ Pulmonary hypertension has been reported to occur in 8% to 84% of patients with IPF, coronary artery disease in approximately 60%, lung cancer in 4.4% to 10%, obstructive sleep apnea in 60% to 90%, and gastroesophageal reflux in 0% to 94%.^{49,50} Conditions such as pulmonary hypertension are associated with greater health care resource utilization, including more diagnostic procedures, therapeutic treatments, and pharmacy claims, which, in turn, imply increased costs.⁴⁹ In the case of pharmacy claims, costs for pulmonary hypertension patients were 6 times higher than those of matched controls with lung disease but no pulmonary hypertension.⁴⁹ The interplay between comorbidities and ILDs also has consequences for prognosis, as fibrotic processes may be a contributing factor in lung cancer, and sleep apnea has been linked to an increased risk of death in patients with IPF.⁵⁰

Depression has been found to be highly prevalent in patients with ILDs. In a study of 52 patients with ILD, depression and anxiety were found in 23% and 27% of patients, respectively. Additionally, abnormalities in sleep quality were observed in 58% of patients.⁵¹ Also, a correlation has been found between diminished functionality (as seen in pulmonary function testing) and subjective breathlessness, with negative impact on quality of life.⁵² Cough and dyspnea can be debilitating, limiting physical activity in performing basic daily tasks, which increases psychological stress.⁵³ When patients with ILDs often feel fatigue, that also negatively affects their quality of life.⁵⁴ And, beyond its clinical impact and influence on quality of life, depression may negatively affect patients' adherence to medical treatment regimens.⁵⁵

The complexity of ILDs with a progressive fibrosis phenotype complicates the ability to understand their economic impact. Nevertheless, costs are significant. Studies examining the impact of IPF on health care resource utilization and costs may provide insights into the impact of non-IPF ILDs with a progressing fibrosis phenotype on these same variables.⁸ More than half of patients with IPF are covered by Medicare.⁵⁶ Based on a random 5% sampling of Medicare beneficiaries between 2000 and 2011, investigators estimated the annual costs attributable to IPF to be \$1.8 billion per year.⁹

In a recent study, investigators assessed the use and costs of health care resources in patients with non-IPF progressive fibrosing ILDs. Findings showed that these patients had higher disease severity and overall health care use compared with patients with non-IPF ILDs. Looking specifically at annual medical costs over a 3-year period, investigators noted that patients with non-IPF progressive fibrosing ILDs averaged \$35,364 in ILD-specific claims, while those in the non-IPF ILD population averaged \$20,211.⁵⁷ Additionally,

the authors noted that in 2016, patients with non-IPF progressive fibrosing ILDs had a mean of 10.5 hospital claims compared with 4.7 among patients with non-IPF ILD.⁵⁷ They concluded that larger-scale investigations are needed to improve understanding of progressive fibrosing ILDs, from the standpoint of both clinical management and associated health costs.⁵⁷

Fibrotic lung disease is also associated with an indirect economic impact, with one study finding that 55% of patients reported illness-related decreased work productivity; this was related to increased absenteeism (~8 hours/week) and presenteeism (~5.5 hours/week).⁵⁸

Treatment Considerations

Historically, the selection of an appropriate treatment for progressive fibrosing ILDs has been challenging because of the absence of effective treatment options and a lack of guideline recommendations. For RA-associated ILD, for example, a lack of sufficient evidence has stymied the development of guidelines for management.⁵⁹ Thus, non-IPF ILDs with a progressive fibrosing phenotype are treated on an empirical basis, often with anti-inflammatory drugs and immunosuppressive agents.⁸

The complexity of non-IPF ILDs with a progressing fibrosis phenotype creates significant challenges for clinicians. Furthermore, their relative rarity frustrates efforts to conduct meaningful research (with implications for trial recruitment), understand these ILDs' natural history, and identify features of disease behavior that inform a detailed description of prognosis, prevalence, and incidence.

For SSC-ILD within 5 years of onset, immunosuppressive therapy with cyclophosphamide was historically used, but now mycophenolate has emerged as the standard of care. Limited evidence shows that the anti-CD20 monoclonal antibody rituximab could be an option for patients with severe fibrotic non-IPF ILD, particularly SSC-ILD, who are unresponsive to conventional immunosuppression.⁶⁰ In a retrospective analysis of 50 patients with varying etiologies, 36 (72%) achieved disease stability or improvement

following administration of rituximab.⁶¹ For patients who have not responded to appropriate treatment, lung transplantation may be an alternative if there are no extrapulmonary contraindications to transplantation.⁶²

In March 2020, nintedanib was approved by the FDA for the treatment of patients with chronic fibrosing ILDs with a progressive phenotype, becoming the first therapeutic agent to receive an indication for this set of diseases. The approval was based on data from the phase 3 randomized, double-blind, placebo-controlled, parallel-group INBUILD trial, which assessed nintedanib in patients with chronic fibrosing ILDs with a progressive phenotype. Patients with non-IPF progressive fibrosis were enrolled⁶³; the most common diagnoses were hypersensitivity pneumonitis and autoimmune disease-associated ILD.⁶³ A similar percentage of patients in the treatment and placebo groups had a UIP pattern (approximately 62%).⁶³ After 52 weeks, the adjusted rate of decline in FVC was significantly lower in the nintedanib group compared with placebo (-80.8 mL/year vs -187.8 mL/year; CI, 65.4-148.5; $P < .001$) in the overall population. Specifically, among patients with a UIP pattern, the declines in FVC were -82.9 mL/year and -211.1 mL/year in the nintedanib and placebo groups, respectively. A benefit for reducing the rate of decline in FVC favoring nintedanib was also demonstrated in patients with other fibrotic patterns.⁶³ The most common adverse event was diarrhea, reported in 66.9% and 23.9% of patients treated with nintedanib and placebo, respectively, with a safety profile consistent with what was previously seen in patients with IPF.⁶³ Although the INBUILD trial was not designed or powered to study individual diseases, prespecified subgroup analyses suggested that the effect of nintedanib was consistent across patients with different ILD diagnoses.⁶⁴

Pirfenidone has also been suggested as a treatment option for progressive fibrosing ILDs. A phase 2 study investigated pirfenidone in patients with unclassifiable progressive fibrosing ILDs.⁶⁵ Although the study did not achieve its primary end point, the authors noted that the secondary end point findings suggest that pirfenidone treatment over a 24-week period may slow disease progression.⁶⁵ After 24 weeks, the mean decline in FVC was lower in patients in the pirfenidone group than patients in the placebo group (-17.8 mL vs -113.0 mL; between-group difference, 95.3 mL [95% CI, 35.9-154.6]; $P = .002$).⁶⁵ Ongoing studies continuing to investigate the potential of pirfenidone include a phase 2 study in patients with RA-ILD (TRAIL1),⁶⁶ which is currently recruiting patients, and Scleroderma Lung Study III, which will assess a combination of pirfenidone with mycophenolate vs mycophenolate alone.⁶⁷

ILD in RA typifies some of the challenging decisions clinicians must make in treating progressing ILD beyond IPF. Typically, intervention is targeted to the inflammatory processes that underlie the pathogenesis of pulmonary manifestations.⁶⁸ Corticosteroids are usually used as first-line treatment, often in conjunction with

other immunosuppressive agents, even though this approach has a lack of clinical evidence in terms of efficacy.⁶⁸ Further complicating treatment is the underlying disease and its treatment. Some disease-modifying antirheumatic drugs, such as methotrexate, leflunomide, and antitumor necrosis factor α , are associated with ILD-promoting effects.⁶⁸

In treating hypersensitivity pneumonitis or ILDs related to occupational exposures, changing the patient's environment is a necessary first step, although this depends on identifying either the inciting antigen or exposure source. Very often, the exposure source is unknown.²⁴

Finally, as stated earlier, patients with ILD have elevated rates of comorbidities, including gastroesophageal reflux, cardiovascular disease, malignancy, sleep apnea, and pulmonary hypertension. In addition to increasing the disease burden, these contribute to hospitalizations, physician visits, and medication use, all of which are associated with cost.⁸ For example, a pathogenic model in which gastroesophageal reflux may contribute to IPF in genetically susceptible individuals has been described.⁶⁹ The WRAP-IPF study assessed whether treatment of abnormal gastroesophageal reflux with laparoscopic antireflux surgery might reduce the rate of IPF disease progression in 58 patients; 29 underwent surgery and 29 who did not. After 48 weeks, those assigned to surgery experienced less decline in FVC (-0.05 L vs -0.13 L).⁷⁰ In addition, there were fewer acute exacerbations, hospitalizations, lung transplantations, and deaths in the surgery group, although these findings did not reach the level of statistical significance.⁷⁰

Discussion and Future Directions

The complexity of non-IPF ILDs with a progressing fibrosis phenotype creates significant challenges for clinicians. Furthermore, their relative rarity frustrates efforts to conduct meaningful research (with implications for trial recruitment), understand these ILDs' natural history, and identify features of disease behavior that inform a detailed description of prognosis, prevalence, and incidence. International guidelines to inform best practices in making a diagnosis and for making treatment decisions would be welcomed, but it is impossible to ignore the practical challenges that would be involved in creating them. Accurate diagnosis may require a multidisciplinary approach, incorporating clinical, pathophysiological, immunological, and imaging information. Comprehensive testing is essential for diagnosis. In a subset of patients with correct diagnoses, appropriate prescription of disease-modifying therapies may offer hope of improvement or resolution of disease.

Treatment for non-IPF ILDs with a progressing phenotype consists mostly of anti-inflammatory and immunosuppressive agents, although only nintedanib is approved with the indication for chronic fibrosing ILDs with progressive fibrosing phenotype.⁸ A new paradigm has emerged, taking into account the similarities

in disease behavior, patterns, and pathogenic mechanisms among fibrotic lung diseases, which all suggest a common treatment pathway.⁷¹ The hallmark UIP pattern in IPF is nonspecific, as it has also been recognized in other ILDs, including CTD-associated ILD, drug-induced ILD, and RA-associated ILD.⁷¹

Questions remain in many relevant areas, including how the cost of medications might be balanced against their effects on disease and comorbidities, patient selection, when to initiate therapy, whether appropriate first- and later-line options exist, and the role of combination therapy strategies. Despite these and other challenges, clinicians are learning how best to use pharmacologic approaches to improve and extend the lives of patients with non-IPF fibrotic ILDs, given the impact of these conditions on morbidity and mortality. ■

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