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Management of Interstitial Lung Disease: Emerging Therapies and Unmet Needs

Interstitial lung disease (ILD) includes more than 200 lung disorders that involve a combination of inflammation and fibrosis of the lung parenchyma.¹ Many patients present with ILDs having a progressive fibrosing phenotype (PF-ILD), which heralds diminished lung function, quality of life, and life expectancy.¹ Although the underlying causes vary, the pathophysiologic mechanisms often overlap, which may enable treatments to work for multiple etiologies of ILD.² In a recent AJMC[®] Peer Exchange™, experts who specialize in treating patients with ILD discussed the clinical burden of the disease; therapeutic strategies for idiopathic pulmonary fibrosis (IPF), non-IPF PF-ILD, and ILD associated with systemic sclerosis (SSc-ILD); and unmet needs for the diagnosis and management of ILD. The session was moderated by **Ryan Haumschild, PharmD, MS, MBA**, director of pharmacy services at Emory Healthcare and Winship Cancer Institute in Atlanta, Georgia.

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EPIDEMIOLOGY AND COMMON CAUSES OF ILD

The incidence and prevalence of ILD vary globally. In a review of epidemiologic studies, the incidence ranged from 1.0 to 31.5 per 100,000 person-years, and the prevalence ranged from 6.27 to 80.9 per 100,000 person-years.³ However, challenges to assessment over time include limitations of methodology, variation in population characteristics, and modifications in the way updated guidelines define ILD subtypes.³

Although ILD has a wide range of etiologies (eg, hypersensitivity pneumonitis, autoimmune conditions), it can also occur without a clear underlying cause (ie, idiopathic disease).^{1,4} IPF is the most common form of idiopathic ILD, and it is progressive.^{5,6} Aberrations in the functioning and signaling of alveolar epithelial cells, interstitial fibroblasts, and immune cells in the lung, which contribute to abnormal proliferation of fibrotic tissue and progressive scarring, are believed to lead to this condition.^{6,7} The risk of developing IPF increases among people aged at least 50 years; men; individuals with a history of cigarette smoking, gastroesophageal reflux disease, chronic viral infections (eg, Epstein-Barr virus), or hepatitis C virus infection; and those with a family history of ILD.⁸

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IPF has a poor prognosis (median survival after diagnosis, 3-5 years), and its vague presentation often leads to a delay in diagnosis.⁵

ILD associated with known causes may also have a progressive fibrosing phenotype that has clinical and mechanistic similarities with IPF.¹ PF-ILD affects approximately 20% to 30% of patients with ILD, although no standardized definition of PF-ILD exists. Several criteria for progression have been proposed based on changes in forced vital capacity (FVC) and diffusing capacity of the lungs for carbon monoxide (DL_{CO}), but the interindividual and intraindividual trajectories of FVC and DL_{CO} vary considerably. Therefore, clinically relevant progression of ILD generally is assessed using a combination of patient-reported symptoms, pulmonary function tests, and imaging findings. Patients with PF-ILD who are at greater risk of progression and death include men, older patients, individuals having a lower FVC and DL_{CO} at baseline, and those with a usual interstitial pneumonia (UIP) pattern on radiology or histology.⁹

Fibrosing ILD, which also is observed frequently in patients with SSC, is the cause of approximately one-third of disease-related deaths.¹ SSC-ILD commonly is characterized by pulmonary fibrosis focused in the basilar parts of the lungs and “Velcro”-like crackles identified on auscultation.¹ SSC typically presents in patients aged 30 to 70 years, and it is 4 times more likely to affect women than men.¹ Patients with SSC-ILD generally have a longer median survival than do those with IPF; the extent of disease on high-resolution computed tomography (HRCT) is an independent prognostic marker.¹

DIAGNOSIS

Diagnosis generally involves evaluations from the departments of pulmonology, radiology, and pathology and includes assessments of clinical presentation, patient history, smoking status, lung function, serologic testing (to assess for underlying autoimmune disease or an autoreactive component), imaging, and lung biopsy (usually only performed if results of other tests are inconclusive).¹ HRCT is the main diagnostic modality; it can be used to estimate prognosis and assess disease progression.¹ The UIP pattern of honeycombing is

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considered to be the “hallmark” for IPF and is essential for a definite diagnosis.⁸ However, the UIP pattern appears to be a particularly strong predictor of prognosis that is observed across ILD subtypes, suggesting that it may be more important for treatment and prognosis than is the etiology of ILD.⁹ In SSC-ILD, HRCT often shows a fibrotic, nonspecific interstitial pneumonia (NSIP) pattern with a relatively high proportion of ground-glass opacities relative to the proportion of course reticulation. However, some patients with SSC-ILD may display a UIP pattern.¹

CLINICAL AND ECONOMIC BURDEN OF ILD

ILD is associated with impaired health-related quality of life (QOL). One study demonstrated that scores on generic and pulmonary-specific QOL questionnaires (eg, Medical Outcomes Study Short Form 36, the Quality of Well-being Scale, the Chronic Respiratory Disease Questionnaire, the St George’s Respiratory Questionnaire) were significantly correlated with measures of respiratory function (6-minute walk test and dyspnea score) in patients with ILD.¹⁰ Additionally, the complexities of diagnosing and managing progressive forms of ILD and the high rate of comorbidities in this population lead to high economic costs and resource use.¹¹ An analysis of claims data from Medicare beneficiaries from 2000 to 2011 showed that, compared with control-matched beneficiaries, individuals with IPF had greater use of health services (eg, hospitalizations, emergency department [ED] visits) during the preindex period (1 year before diagnosis) and postindex period (1 year after diagnosis) ($P < .01$ for all).¹¹

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Among patients with IPF, total medical costs were 72% and 134% higher during the preindex and postindex periods, respectively, with higher costs present across all health care settings.¹¹

STAKEHOLDER INSIGHTS

Identification of the type and cause of ILD is important, because the prognosis and approach to treatment vary. However, there is considerable “gray area” among the forms of ILD. Many types of ILD share fibrosis as a common pathway, but identification of patients with a significant inflammatory component can be useful for determining patients who may benefit from immunosuppressive therapies, according to **Kristin Highland, MD**, director of the rheumatic lung disease program at the Cleveland Clinic in Cleveland, Ohio.

Early referral to a center with clinicians experienced in evaluating patients with ILD is likely to optimize patient outcomes, because these providers can identify a need for surgical biopsies and the ability to be safely observed without medications, said **Daniel Culver, DO**, chair of the department of Pulmonary Medicine at the Cleveland Clinic in Cleveland, Ohio. “There are delays at every single step of the [referral] process,” he said. “By the time they get to us ... we really [want to] accelerate the process, so having the chance to get the appropriate testing done without a lot of negotiations with payers is always really well-appreciated by [the patient and] us.”

Culver added that whereas optimal treatment of ILD involves collaboration among providers from multiple specialties, pulmonologists have a central role in determining whether a patient is likely to benefit from antifibrotic medications or drugs used to manage pulmonary hypertension. In addition to requiring a multidisciplinary approach to management, noted Highland, ILD places a substantial burden on QOL, with many patients being anxious about disease outcomes and experiencing significant physical limitations that decrease their independence.

In addition to the clinical burden, the economic burden of ILD is substantial and increased when patients receive suboptimal treatment, according to Haumschild. “Having that right specialist manage the patient means less ED utilization, less outpatient utilization, and better QOL,” he said. “When we look at some of these health care utilizations, ... when we look at some of the related costs, we see that cost increase over time ... because patients may not have great adherence to therapies, they may not feel like their condition is controlled, or they may have other disease manifestations.” He added that payers also try to find ways of treating patients on a large scale to avoid duplication of services, because many patients with ILD have other comorbidities (eg, depression, anxiety) that require additional treatment. Further,

awareness of ILD, particularly in terms of QOL, is low among payers, health plans, and employer groups. Finding ways to reduce presenteeism and absenteeism and better manage the disease is likely to improve QOL for the patient and caregiver and enhance productivity and staffing in employer groups.

Highland added that improving access to pulmonary rehabilitation can improve exercise tolerance, QOL, and independence, and these ancillary services are important to consider along with use of medications. Palliative medicine is another important component that is instrumental for maximizing patient QOL and management of care costs by keeping patients out of the hospital and ED, according to Culver.

PHARMACOLOGIC TREATMENT OF ILD

The general approach for treating patients with ILD involves antifibrotic therapy for IPF and immunosuppressive therapies for non-IPF ILD.⁹ Identification of IPF is important because of the potential harm in treating affected patients with immunosuppressive therapies; however, antifibrotic therapies may benefit patients who have non-IPF ILDs with a progressing phenotype, including those caused by autoimmune conditions (eg, SSc), hypersensitivity pneumonitis, and idiopathic NSIP, because they have similar pathophysiologic mechanisms of disease.^{2,9}

IPF

Nintedanib and pirfenidone are treatments approved for use in patients with IPF.^{12,13} The phase 3 INPULSIS-1 and INPULSIS-2 trials (NCT01335464 and NCT01335477, respectively) showed that patients with IPF who received nintedanib had a significantly lower adjusted annual rate of change in FVC compared with those given placebo.⁷ In the INPULSIS-1 trial, the annual rate of change in FVC was -114.7 mL per year in the nintedanib group and -239.9 mL per year in the placebo group (difference, 125.3 mL per year; 95% CI, 77.7-172.8; $P < .001$); and in the INPULSIS-2 trial, the rate of change was -113.6 mL per year in the nintedanib group and -207.3 mL per year in the placebo group (difference, 93.7 mL per year; 95% CI, 44.8-142.7; $P < .001$).⁷ Diarrhea (mostly of mild to moderate intensity) was the most frequently reported adverse event (AE); it occurred in 61.5% and 63.2% of the nintedanib groups in the INPULSIS-1 and INPULSIS-2 trials, respectively, and 18.6% and 18.3% of the placebo groups, respectively.⁷ Premature discontinuation of study treatment due to diarrhea occurred in 4.5% (INPULSIS-1) and 4.3% (INPULSIS-2) of patients given nintedanib and none (INPULSIS-1) and 0.5% (INPULSIS-2) of those given placebo.⁷ Elevations in liver enzymes were also more frequent with use of nintedanib than placebo (INPULSIS-1, 4.9% vs 0.5%, respectively; INPULSIS-2, 5.2% vs 0.9%, respectively).⁷

Pirfenidone also showed promising efficacy for patients with IPF in the phase 3 ASCEND trial (NCT01366209), with a 47.9% reduction in the proportion of patients who had a decline of at least 10 percentage points in predicted FVC or who died by 52 weeks (16.5% vs 31.8% with placebo).¹⁴ The pirfenidone group had higher rates of gastrointestinal (GI) and skin-related events compared with those in the placebo group; however, these AEs were often mild to moderate in severity and reversible, and they did not result in any clinically significant complications.¹⁴ In the pirfenidone group, 2.2% and 2.9% of patients

discontinued therapy due to GI and skin-related toxicities, respectively; in the placebo group, these AEs led to treatment discontinuation among 1.1% and 0.4% of patients, respectively.¹⁴

PF-ILD

PF-ILD has similar clinical and pathophysiologic features to IPF, and it was recently proposed that antifibrotic treatments used for IPF could be effective for PF-ILD.² In 2020, nintedanib became the first FDA-approved treatment for ILDs that have a progressive phenotype (ie, those caused by autoimmune conditions, hypersensitivity pneumonitis, and idiopathic NSIP).¹⁵

In the phase 3 INBUILD trial (NCT02999178), patients with ILD having a progressive fibrotic phenotype other than IPF were randomly assigned to receive nintedanib or placebo. The adjusted rate of FVC decline over 52 weeks was less with nintedanib than with placebo in the overall population (-80.9 vs -187.8 mL per year, respectively; between-group difference, 107.0 mL per year; 95% CI, 65.4 - 148.5 ; $P < .001$), the group with an UIP-like fibrotic pattern (-82.9 vs -211.1 mL per year; difference, 128.2 mL per year; 95% CI, 70.8 - 185.6 ; $P < .001$), and the group with other fibrotic patterns (-79.0 vs -154.2 mL per year; difference, 75.3 mL per year; 95% CI, 15.5 - 135.0).² Similar to findings of the IMPULSIS trials, diarrhea was the most frequent AE reported; it occurred in 66.9% and 23.9% of the nintedanib and placebo groups, respectively, and elevations in liver enzymes (more than 3 times the upper limit of normal) occurred in 13.0% and 1.8% of the nintedanib and placebo groups, respectively.^{2,7} The nintedanib group, as compared with the placebo group, also had a higher proportion of patients with AEs leading to a permanent dose reduction (33.1% vs 4.2%, respectively) or discontinuation of therapy (19.6% vs 10.3%).²

The annual rates of FVC decline with placebo and the absolute treatment effects of nintedanib in patients with PF-ILD were similar to those observed in IPF populations. This suggested that the pathobiologic mechanisms and responses to antifibrotic therapies are similar among ILDs with a progressive fibrosing phenotype regardless of the underlying cause.²

Pirfenidone was also studied in patients with non-IPF PF-ILD (connective tissue disease-associated ILD, fibrotic NSIP, chronic hypersensitivity pneumonitis, or asbestos-induced lung fibrosis) in the phase 2b RELIEF trial (NCT03099187). According to the rank analysis of covariance for the primary end point (absolute change in percentage of predicted FVC from baseline to week 48) with diagnostic group as a factor, the decline in percentage of predicted FVC was significantly less with pirfenidone than with placebo ($P = .043$). Reported GI AEs occurred slightly more frequently, and dyspnea and respiratory tract infections were slightly less common, in the pirfenidone group than the placebo group. The authors stated that the results should be interpreted cautiously because of early trial termination (due to slow recruitment), but they noted that pirfenidone showed promising benefits in lung function in this patient population.¹⁶

SSc-ILD

Cyclophosphamide was one of the initial immunosuppressive therapies that showed promise for SSc-ILD based on outcomes from the

Scleroderma Lung Study I (NCT00004563), which compared 1 year of cyclophosphamide therapy with placebo use. A modest mean absolute difference in FVC at 12 months (after adjustment for baseline FVC) that favored cyclophosphamide (difference, 2.53%; 95% CI, 0.28%-4.79%; $P < .03$) was noted.¹⁷ However, acute toxicity is common with cyclophosphamide, and hematuria, leukopenia, neutropenia, anemia, and pneumonia occurred more often in the cyclophosphamide group during the first year. Additionally, long-term use of cyclophosphamide may increase the risk for malignancies.^{17,18}

Mycophenolate mofetil (MMF), which has a relatively favorable safety profile and provides effective immunosuppression in patients with SSc-ILD, was compared with cyclophosphamide in the Scleroderma Lung Study II (NCT00883129). No difference in the predicted percentages of FVC was observed between 24 months of MMF and 12 months of cyclophosphamide plus 12 months of placebo (average improvement at 24 months, 2.19%-predicted [95% CI, 1.53%-3.84%] and 2.88%-predicted [95% CI, 1.19%-4.58%], respectively). However, leukopenia (30 patients vs 4 patients; $P < .05$) and thrombocytopenia (4 patients vs 0 patients; $P < .05$) were more common among the cyclophosphamide group, and time to medication withdrawal or treatment failure was shorter in the cyclophosphamide group ($P = .019$). Therefore, MMF appeared to be a better tolerated option for immunosuppression, but it had similar efficacy in improving FVC.¹⁸

SSc-ILD and IPF share some pathophysiologic mechanisms (eg, excess production of extracellular matrix and conversion of fibroblasts to a myofibroblastic phenotype); therefore, nintedanib was believed to be a promising therapeutic option to address the progressive fibrosis component. The phase 3 SENSICIS trial (NCT02597933) of patients with SSc-ILD showed that the adjusted annual rate of change in FVC was lower with nintedanib than with placebo (-52.4 vs -93.3 mL per year; difference, 41.0 mL per year; 95% CI, 2.9 - 79.0 ; $P = .04$). Similar to results of other trials of nintedanib, diarrhea was the most common AE, occurring in 75.7% and 31.6% of the nintedanib and placebo groups, respectively. Elevations of at least 3 times the upper limit of normal in alanine aminotransferase, aspartate aminotransferase, or both occurred in 4.9% and 0.7% of patients given nintedanib or placebo, respectively.¹⁹

A prespecified subgroup analysis of data from the SENSICIS trial demonstrated that patients taking MMF tended to have a less rapid decline in FVC. The annual rates of change among those receiving MMF at baseline were -40.2 mL per year and -66.5 mL per year in the nintedanib and placebo groups, respectively, compared with -63.9 mL per year and -119.3 mL per year in those given nintedanib or placebo but not MMF.¹⁹ The results indicated that MMF may have a beneficial effect

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on lung function in patients taking MMF; however, the investigators cautioned about limitations associated with comparing these groups, because patients did not undergo randomization according to MMF use.¹⁹ The phase 2 Scleroderma Lung Study III (NCT03221257) is active and is designed to compare the addition of pirfenidone or placebo to background MMF therapy in patients with SSC-ILD.²⁰

Because patients with SSC have elevated circulating levels of interleukin-6 (IL-6), which may contribute to skin fibrosis and SSC-ILD, use of the IL-6 inhibitor tocilizumab has been proposed as an option to address these conditions.²¹ The primary end point of the phase 3 focuSSced trial (NCT02453256), the changes in skin fibrosis (via the change in modified Rodnan skin score from baseline to week 48), was not met—the least-squares mean change in predicted percentage of FVC from baseline to week 48 was lower in the tocilizumab group (−0.4 vs −4.6 in the placebo group; difference, 4.2; 95% CI, 2.0–6.4; $P = .0002$).²¹ According to the investigators, tocilizumab may be a promising option to minimize loss of lung function in patients with early-stage SSC.²¹

STAKEHOLDER INSIGHTS

Consideration of an antifibrotic agent such as nintedanib or pirfenidone is important if the patient is suspected to have IPF, noted **Paul Noble, MD**, Vera and Paul Guerin Family Distinguished Chair of pulmonary medicine at Cedars-Sinai Medical Center in Los Angeles, California. However, he continued, agents targeting the immune system (eg, steroids and steroid-sparing agents that include MMF) often can prevent progression and delay the need for antifibrotic agents in patients with ILD caused by hypersensitivity pneumonitis or a connective tissue disorder. He recounted, “I’ve had patients that I’ve followed for upwards of 20 years who’ve had a stable connective tissue disease and never [have] gone on to need a lung transplant. With the progressive phenotype, the argument from some of the pharmaceutical companies is [to] put everybody on [an] antifibrotic. My concern with that is [that] if you miss the underlying cause, you’re keeping that patient from the opportunity of getting better, because the antifibrotics don’t make you better.”

Culver said that he discusses both nintedanib and pirfenidone with all of his patients with IPF, even those with mild or early-stage disease, and noted that the therapeutic selection largely is based upon the individual patient’s willingness to tolerate the drug’s AE profile. “I don’t think that today we can say convincingly that 1 of the 2 agents is head-and-shoulders ahead of the other one in terms of efficacy,” he acknowledged.

Noble indicated that he considers nintedanib use in patients with ILD that progresses during immunosuppressive therapy. Further, he noted that maintaining immunosuppression with antifibrotic therapy is reasonable, considering the lower decline in lung function observed among patients with SSC-ILD who were taking MMF with nintedanib in the SENSICIS trial. Highland added that patients with SSC-ILD also tend to be younger than are those with IPF and have more potential years of life left—therapies such as nintedanib can produce a small reduction in FVC decline that can add up over time.

Culver noted that data supporting pirfenidone and nintedanib, particularly for IPF, are highly robust, with more than 1300 patients enrolled across key registration trials. Additionally, real-world data revealed since those trials, along with results from European registries, suggest that these agents are associated with a reduction in risk of death. However, he noted that clinical benefits still could be improved.

Many of the newer agents used for ILD (eg, nintedanib, pirfenidone, and tocilizumab), noted Highland, have a higher financial cost. Further, they are distributed through specialty pharmacies that have staff who are knowledgeable about navigating prior authorization procedures, finding patient assistance programs, and monitoring drug toxicities. However, she expressed her frustration with the need to resubmit prior authorizations at the beginning of each calendar year, which can be inconvenient for patients and providers. “Once [patients with ILD are] on a drug,” she said, “they probably should be able to stay on the drug, [as] their diagnosis of ILD hasn’t changed.”

EMERGING THERAPIES AND UNMET NEEDS IN ILD

Whereas robust data are available for IPF and SSC-ILD, stated Highland, data on other types of ILD are sparse, because they are less common and more heterogeneous. However, she added, the ability to group patients based on pathophysiology is encouraging and may allow for application of data and translation of therapy to multiple subtypes. Use of precision medicine to identify biomarkers that predict progression and response to therapy is also essential, she said.

Noble added that finding therapeutic approaches that target the abnormal alveolar type 2 cells seen in IPF could help improve FVC, and having better-tolerated agents that patients could take for several years could improve overall outcomes.

Culver noted that therapies targeting multiple parts of the pathophysiology of ILD are likely needed to improve ILD outcomes. Patient referral to centers of excellence, he concluded, would also improve access to effective therapies and diagnostics, enhance quality of care, and reduce costs. •

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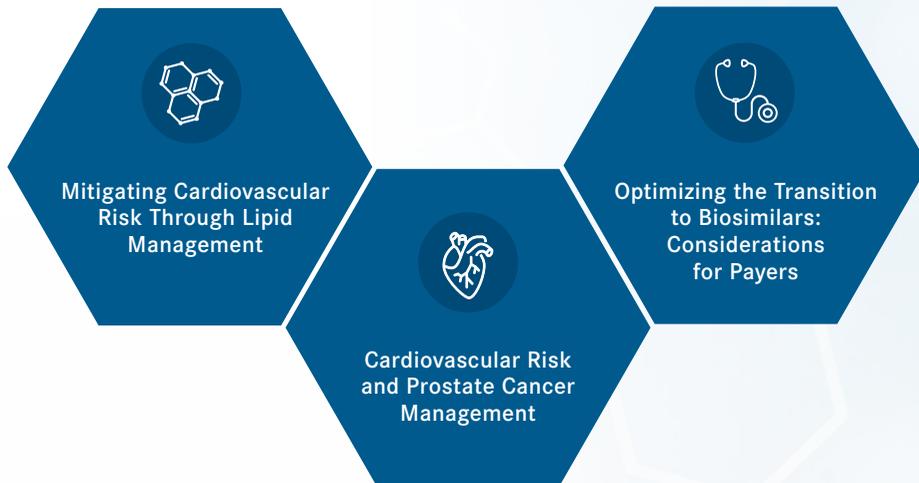
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