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Antifibrotics in Non-Idiopathic Pulmonary Fibrosis Interstitial Lung Diseases

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Case 1

A 73-year-old male with a history of seronegative rheumatoid arthritis associated interstitial lung disease (RA-ILD), showing a probable usual interstitial pneumonia pattern of fibrosis, was seen for follow up. He had initially been started on mycophenolate for treatment of his ILD and remained stable on this treatment for a period; however, he later experienced slowly worsening dyspnea and cough over time. His pulmonary function tests (PFTs) demonstrated a 9.5% relative and 6% absolute decline in forced vital capacity (FVC) and a 12% relative and 10% absolute decline in diffusion capacity for carbon monoxide (DLCO) over the past 20 months. A computed tomography (CT) scan of the thorax showed some new changes of mild honeycombing in the right lower lobe **(Figure 1)**.

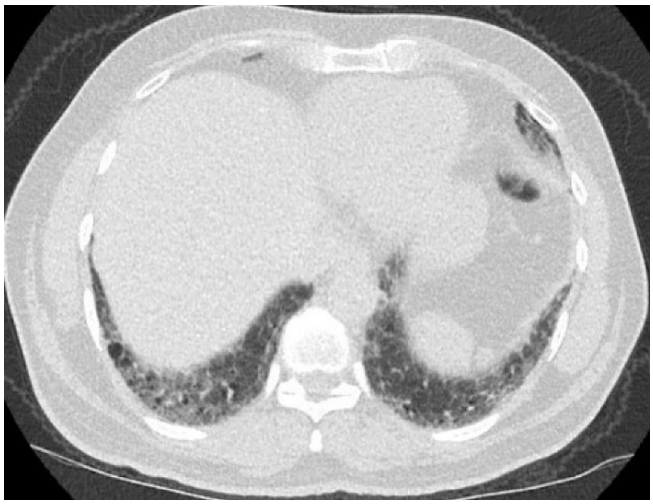

Figure 1. Axial view of recent CT thorax demonstrating new mild honeycombing in the right lower lobe; *courtesy of Yassmin Behzadian, MD, FRCPC, and Ambrose Lau, MD, MEd, FRCPC*

Case 2

A 50-year-old male developed dyspnea and cough after a COVID-19 infection. During the COVID-19 infection, his symptoms were mild and did not require treatment or hospitalization. A CT scan of the thorax demonstrated evidence of a fibrotic non-specific interstitial pneumonia pattern. Subsequent evaluation for new-onset ILD, included a surgical lung biopsy, which demonstrated organizing pneumonia with cicatricial changes.

The patient received a course of prednisone, which led to a significant improvement in his symptoms but no improvement in imaging or PFTs. After tapering off prednisone, he required another course due to re-emergence of symptoms. However, retreatment yielded no improvement in his symptoms, imaging, or PFTs. The patient's case, imaging, and pathology were reviewed in a multidisciplinary discussion, resulting in a diagnosis of organizing pneumonia evolving

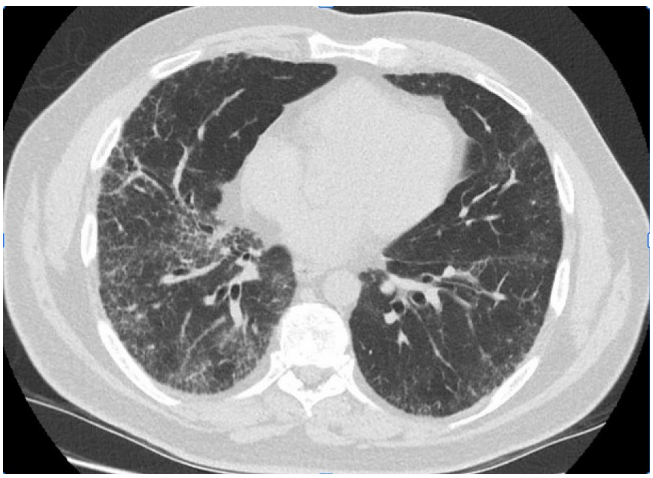

Figure 2. Axial view of recent CT thorax demonstrating increased reticulation; *courtesy of Yassmin Behzadian, MD, FRCPC, and Ambrose Lau, MD, MEd, FRCPC*

toward a more fibrotic phenotype. In addition to his worsening symptoms, imaging revealed increased reticulation, and assessments showed a significant decline in his FVC and DLCO over time.

Progressive Pulmonary Fibrosis

ILDs comprise a group of parenchymal pulmonary diseases with diverse causes and manifestations. In addition to Idiopathic Pulmonary Fibrosis (IPF), numerous other types of fibrotic ILDs exist. Progressive pulmonary fibrosis (PPF) is a possible disease course in these non-IPF fibrotic ILDs, characterized by progression over time.[1]

The 2022 American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), Asociación Latinoamericana de Tórax (ALAT) clinical practice guideline defines PPF as the presence of at least two out of three criteria occurring within the past year, with no other cause: 1) worsening respiratory symptoms, 2) physiological disease progression, and 3) radiological disease progression.[1] It is important to note that definitions of progression vary in the literature. For example, the INBUILD trial defined progression as any of the following occurring within the previous 24 months: a relative decline in FVC of ≥10% of the predicted value, a combination of a relative decline in the FVC of 5% to <10% of the predicted value combined with increased respiratory symptoms or fibrosis extent on high-resolution CT (HRCT), or increased respiratory symptoms and fibrosis extent on HRCT.[2] The 2022 ATS/ERS/JRS/ALAT clinical practice guideline defines physiological disease progression as either an absolute decline in FVC of ≥5% predicted or an absolute decline in DLCO (hemoglobin-corrected) of ≥10% predicted within 1 year.[1] A comparison of these and other criteria is outside the scope of this paper.

The reported prevalence of PPF varies across studies and is dependent on various factors, such as the definition of progression used and the type of ILD. A recent retrospective analysis noted a PPF prevalence of 40% when using the 2022 ATS/ERS/JRS/ALAT criteria.[3] Patients who experience progression have early mortality and an overall disease course that is similar to that of patients with IPF.[4]

The Use of Antifibrotics in Non-Idiopathic Pulmonary Fibrosis Interstitial Lung Diseases

The available antifibrotics currently approved for the treatment of IPF include nintedanib and pirfenidone, with the former also being approved by Health Canada for the treatment of PPF.

Nintedanib is an oral tyrosine kinase inhibitor that binds and blocks multiple receptors to ultimately suppress central processes involved in fibrosis.[5] The INPULSIS-1 and INPULSIS-2 trials assessed the role of nintedanib in the treatment of IPF, demonstrating that nintedanib reduced the annual rate of FVC decline compared to placebo.[6]

Subsequent studies have assessed the role of nintedanib in the treatment of patients with non-IPF ILDs. The SENSCIS trial was a randomized, double-blind, placebo-controlled, phase 3 study that evaluated the impact of nintedanib on the annual rate of FVC decline over 52 weeks in patients with systemic sclerosis associated ILD (SSc-ILD). Enrolled patients had at least 10% fibrotic lung involvement on high-resolution CT scans, among other inclusion criteria.[7] Patients treated with nintedanib experienced a significant reduction in the annual rate of FVC decline compared to placebo.[7] In the SENSCIS trial, 48.4% of patients were receiving background mycophenolate therapy at baseline.[7] A subsequent post hoc analysis found that nintedanib's effect on the attenuation of annual FVC decline was not significantly influenced by concomitant background mycophenolate therapy.[8]

The INBUILD trial, which was a randomized, double-blind, placebo-controlled phase 3 study, assessed the effect of nintedanib in patients with non-IPF fibrotic lung disease and evidence of progression. Patients who received nintedanib demonstrated a significant reduction in the annual rate of FVC decline compared to placebo.[2] A post hoc analysis of this trial suggested that nintedanib exerted a consistent effect on the annual rate of FVC decline across patients with the various ILD diagnoses included.[9] Diarrhea was the most frequently reported adverse event among patients receiving nintedanib in the INBUILD, INPULSIS, and SENSCIS trials.[2,6,7]

Pirfenidone is an oral antifibrotic currently used in the treatment of patients with IPF and has been shown to reduce disease progression in this patient population compared to placebo.10 The use of pirfenidone in patients with non-

IPF fibrotic ILDs has also been assessed. The RELIEF study suggested that pirfenidone may help reduce disease progression in patients with certain non-IPF fibrotic ILDs exhibiting evidence of progression.[11] In the TRAIL1 trial, the composite primary endpoint, defined as a decline in percent predicted FVC of at least 10% from baseline or death, was not significantly different between patients with RA-ILD receiving pirfenidone or placebo. However, patients with RA-ILD who received pirfenidone exhibited a lower annual rate of FVC decline.[12] Both these studies were terminated early due to various challenges, which limits the interpretation of results.[11,12]

Nerandomilast, an oral phosphodiesterase 4B inhibitor, has antifibrotic and immunomodulatory properties. Recent double-blind, randomized, placebo-controlled phase 3 trials demonstrated that nerandomilast attenuated FVC decline over 52 weeks compared to placebo in patients with IPF[13] as well as in patients with other fibrotic lung diseases showing evidence of progression.[14] In the latter population, 43.5% of patients were receiving background nintedanib.[14]

Review of Cases

In case 1, the patient demonstrated evidence of PPF based on worsening symptoms and radiological evidence of fibrotic progression. Additionally, there was a documented decline in both FVC and DLCO over time.

In patients with fibrotic ILD, nintedanib is often initiated in a stepwise approach. The 2022 ATS/ERS/JRS/ALAT clinical practice guideline suggests the use of nintedanib in patients with fibrotic lung disease with PPF who do not respond to standard management, which may include non-pharmacological and/or pharmacological strategies, and which will vary based on the underlying ILD and the specific context.[1]

In this case, initiation of antifibrotic therapy over increasing the patient's immunosuppressive therapy was recommended, as the patient exhibited evidence of a fibrotic ILD with fibrotic progression despite treatment, and no evidence of an alternative cause (e.g., poorly controlled inflammation) based on available investigations. For some patients with RA-ILD, who present with predominantly fibrotic disease at diagnosis, have already demonstrated progression, and who show minimal concern for an active inflammatory process, it may be reasonable to consider upfront initiation of nintedanib versus immunosuppressive therapy. However, the 2023 guideline from the American College of Rheumatology (ACR)/ American College of Chest Physicians (CHEST) on managing patients with systemic autoimmune rheumatic disease associated-ILD, a consensus was not reached regarding nintedanib as a first line treatment option in RA-ILD.[15]

In case 2, given the progression of the patient's symptoms, declining PFTs over time, and increased reticulation on imaging, antifibrotic treatment with nintedanib was recommended. Immunosuppressive therapy could also be reassessed in the future should the patient develop inflammatory changes or a connective tissue disease. Case 2 demonstrates the role of nintedanib in managing patients who have non-IPF fibrotic lung disease with PPF when no alternative cause is suspected. It also highlights the importance of multidisciplinary discussion in diagnosis and during management decisions, especially for patients with ILD.

Conclusion

For patients with non-IPF fibrotic lung disease, the current guideline recommends nintedanib for patients with evidence of PPF.[1] Pirfenidone has also been studied and shows supportive findings, though interpretation of the data is more limited. Nerandomilast, pending Health Canada approval, has shown a decrease in FVC decline compared to placebo in this patient population.[14]

The use of antifibrotics in patients with non-IPF fibrotic lung diseases should be individualized, taking into account the patient's clinical history, personal preferences, and, whenever possible, input from a multidisciplinary discussion.

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As with any case study, the results should not be interpreted as a guarantee or warranty of comparable results. Individual results may vary depending on the patient's circumstances and condition.