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COMMENT

A role of antifibrotics in the treatment of Scleroderma-ILD?

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Systemic sclerosis (SSc) is a complex potentially life-threatening autoimmune disease. Interstitial Lung Disease (ILD) is a rather common manifestation of the disease,[1] which governs morbidity and mortality, accounting for 33% of deaths.[2] The spectrum of ILD ranges from limited lung disease, with or without clinical significance, to severe fibrosis and respiratory failure.[1–3] Histopathologic subsets and imaging features of SSc-ILDs, mainly non-specific interstitial pneumonia, are related to disease outcome.[4]

While no therapeutic algorithm exists, treatment decisions are based generally on disease activity, disease extent and progression, whilst some expert physicians support the ''active surveillance'' approach. Merely disease extent is not a widely recognised marker for treatment initiation, as some patients with extensive disease remain stable, whilst others with limited disease, experience significant decline.

Intriguingly, ILD treatment remains challenging with no licensed therapeutic regimen. Therapy of SSc-ILD centres on controlling the inflammatory process that precedes and leads to the initiation and, partially, the progression of fibrosis. Inflammation is a targetable endpoint during the inflammatory phase before the irreversible established fibrosis. Clinical studies in Idiopathic Pulmonary Fibrosis (IPF), the most well studied ILD, have shown that fibrosis does not respond to anti-inflammatory medication and can be detrimental, when inflammation is not the predominant element.[5]

To date, the therapeutic strategy for SSc-ILD involves induction and maintenance of remission. Cyclophosphamide (CYC) and Mycophenolate mofetil (MMF) are the two agents most commonly used. A meta-analysis of three randomized trials and six open label studies did not confirm an improvement in pulmonary function with cyclophosphamide after 12 months.[6] Toxicity issues have led trials of other immunosuppressants as possible alternatives. MMF was found non-inferior to CYC, with a better tolerability profile. Both treatment options seemed to have an impact on other clinical parameters like the modified Rodnan Skin Score (mRSS).[7] As immunosuppressive therapy exerts its effects on inflammatory processes, it has limited benefit

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on the fibrotic process. The proportion of patients that develop a progressive fibrotic phenotype, resembling that of IPF despite immunosuppressive treatment, characteristically emphasises the great unmet need in the treatment of SSc-ILD.

In the era of novel antifibrotics, licenced for the treatment of IPF, it is tempting to speculate that these agents may have a place in the treatment of other fibrotic ILDs. Indeed, studies regarding the pathogenesis behind other ILDs dictate a possible common pathway that lead to fibrosis, after the initial insult. In all ILDs, wound healing is aberrant and leads to scarring. Following tissue injury, fibroblasts and monocytes are recruited at site. Fibroblasts are activated to become myofibroblasts, the key extracellular matrix (ECM) producing cells, under the influence of pro-fibrotic monocytes and macrophages.[8]

Nintedanib is a tyrosine kinase inhibitor that targets the receptors platelet-derived growth factor receptor α and β, fibroblast growth factor receptor (FGFR) 1–3, and vascular endothelial growth factor receptor (VEGFR) that slows disease progression in patients with IPF, by reducing the annual rate of decline in forced vital capacity (FVC). Tyrosine kinases are enzymes that regulate important cellular functions, including survival, proliferation and differentiation.[9] Nintedanib inhibits progressive lung fibrosis by inhibiting fibroblast proliferation[10,11] and it has been shown to inhibit pro-fibrotic M2 polarization of macrophages.[12] The promising results that were obtained in open label trials of the first marketed inhibitor of tyrosine kinase, namely Imatinib[13] has led several trials to be designed to investigate the efficacy of antifibrotics in other ILDs.

The recently published SENSIS trial is the first to prove that Nintedanib is efficacious in the treatment of SSc-ILD in combination with background immunosuppressant therapy.[14] These results encourage the upcoming trials in other progressive fibrotic ILDs,[15] where immunosuppressive and antifibrotics are combined. However, the results should be interpreted with caution. The clinical significance of an average treatment benefit of only 41 mL lies at the lower end of the minimally important clinical difference in IPF studies and is difficult to interpret.[16] We believe that these findings do not justify first line use of Nintedanib as Mycophenolate Mofetil may be equally efficacious in SSc-ILD and has treatment benefits for systemic disease activity.

Furthermore, the small FVC treatment effect may be a misleading average statement, concealing major benefits in a minority patient sub-group with progressive disease. Nintedanib may have an important future role in patients with more extensive disease on high-resolution computed tomography (HRCT), at higher risk of disease progression. However, if sub-analyses in higher risk disease are to be informative, the methodology of HRCT scoring will need to be scrutinized. Based on other series,[17] the HRCT extent of SSc-ILD was strikingly higher than expected from the stated FVC and Diffusing capacity of the lung for carbon monoxide (DL_{CO}) values.

In conclusion, the diagnosis of ILD alone may not be considered adequate for the initiation of anti-fibrotic therapy in SSc. Accurate staging of the ILD, with respect to disease behavior may be required to identify the sub-group of patients that would benefit more from antifibrotic therapy.

Conflict of interest

The authors have no conflicts of interest to declare.

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