The challenge of evidence-based therapy for lung fibrosis in systemic sclerosis

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An excellent review of systemic sclerosis (scleroderma, SSc) associated lung fibrosis included in this issue [1] is testament to the large body of work over several decades that has helped to better define the frequency, impact and management of lung fibrosis in this disease. Translational research has also elucidated key aspects of aetiopathogenesis. The progression of lung fibrosis in SSc is highly variable and we are now able to identify patients most at risk for severe lung fibrosis and determine cases more likely to have an indolent course based on clinical and laboratory characteristics [2]. There are important shared mechanisms that underpin progression of lung fibrosis and its clinical impact that also operate in idiopathic pulmonary fibrosis (IPF) and in other types of progressive interstitial lung disease. These processes are likely to be the explanation for congruent treatment benefit from nintedanib that has recently been shown to reduce the rate of progression of lung fibrosis in SSc [3] and other forms of progressive lung fibrosis [4] building upon the platform of established clinical benefit for antifibrotic drugs such as nintedanib and pirfenidone in IPF.

There are also some important differences between SSc associated lung fibrosis and IPF. These include a much lower rate of overall progression and better survival for SSc associated lung fibrosis. Nevertheless, lung fibrosis remains a major cause of death in SSc and the most serious cases have dreadful prognosis. Another difference from IPF is that there is now strong evidence supporting benefit for immunosuppression in SSc associated lung fibrosis. This comes from placebo-controlled trials of oral [5] or intravenous cyclophosphamide [6] and from studies of mycophenolate mofetil [7]. The recent SENSCIS trial also reported greater numerical benefit for cases receiving mycophenolate as well as nintedanib [3]. More targeted biological approaches may also be effective and there is robust evidence from clinical trials that IL6 receptor blockade substantially reduces the progression of early lung fibrosis in high risk cases of SSc from robust clinical trials that failed to show major impact on skin fibrosis [8]. However, antifibrotic agents and immunosuppressive drugs have well recognised potential toxicity and this needs to be balanced against the relatively modest group level treatment effect in SSc associated lung fibrosis trials.

In an era of evidence-based medicine and harmonisation of best practice, emerging high-quality evidence about outcome, pathogenesis and treatment impact is very welcome. At the same time, it may cause some consternation for clinicians trying to balance risk and benefit of therapy at an individual patient level, as well as the substantial economic burden of high cost drugs to the healthcare system. The high cost of biologics should also be considered against the cost of lung transplant and haemopoietic stem cell transplantation in those individuals deemed appropriate after careful assessment of SSc associated comorbidities.

On a practical level, clinicians need to know when to start treatment, who to target and how to combine different drugs. We have learned from other disease areas like cancer and from managing commoner rheumatic disease such as rheumatoid arthritis that combining drugs with complementary modes of action can deliver better and more durable clinical benefit. This will be the next major challenge for treatment of SSc associated lung fibrosis. In addition, we should identify cases that are most likely to progress and develop better markers and predictors that can be applied in practice. Critically, we will harness the collective expertise of colleagues in rheumatology and respiratory medicine working together and it is encouraging to see that this is already happening across centres with specialised interest in connective tissue diseases. European consensus recommendations for management of SSc associated lung fibrosis are being proposed and will soon be published [9]. Although undoubtedly these will need revision and refinement as new evidence emerges it will provide a good starting point for the progress in management that is much needed and that our patients deserve.

As a complex multifaceted disease, SSc requires stage-specific approaches that reflect the key driving pathogenic processes to manage major organ-based complications. Historically, scleroderma renal crisis became the first severe manifestation to be treatable. Some decades later, pulmonary arterial hypertension has become a manageable complication, albeit one that requires early use of combination therapy to maximise benefit [10]. We are now at the dawn of an era with lung fibrosis as the next major life-threatening aspect of SSc to be yielding its secrets. This is cause for cautious optimism but the next steps in terms of clinical trial design and education of clinicians and patients are critical. One notable difference between the vascular complications and lung fibrosis is that tackling fibrosis may have a much more generalisable benefit for other organ based and skin disease in SSc and so there is potentially greater opportunity but also higher risk. The potential toxicity of effective antifibrotic agents targeting processes that are central to normal wound healing and repair, especially in combination with powerful immunosuppressive drugs should not be overlooked. In addition, cost-effectiveness of these approaches needs to be carefully evaluated. Expectations need to be managed so that modest success observed in recent clinical trials is recognised as only the first step towards major clinical progress in this area of high unmet need.

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