Interstitial lung disease in systemic sclerosis

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Summary

Based on international collaborative data, interstitial lung disease is now the most frequent cause of death in systemic sclerosis (SSc), having supplanted renal crisis in that regard. Despite detailed explorations of candidate mediators, no primary pathway in the pathogenesis of interstitial lung disease associated with SSc (SSc-ILD) has been definitively identified and, therefore, treatment with current agents is only partially successful. However, as immunomodulatory agents do, on average, retard progression of lung disease, early identification of SSc-ILD using thoracic high resolution computed tomography (HRCT), is highly desirable. The decision whether to introduce therapy immediately is often difficult as the balance of risk and benefit favours a strategy of careful observation when lung disease is very limited, especially in longstanding SSc. The threshold for initiating treatment is substantially reduced when lung disease is severe, systemic disease is short in duration or ongoing progression is evident, based on pulmonary function tests and symptoms. This review summarises epidemiology, pathogenesis, difficult clinical problems and management issues in SSc-ILD.

Interstitial lung disease associated with systemic sclerosis (SSc-ILD) is now the major cause of death in systemic sclerosis (SSc), due to respiratory failure or fatal pulmonary hypertension. Despite advances in our understanding of the epidemiology and pathogenesis of SSc-ILD, there are major ongoing uncertainties regarding key pathogenetic pathways. Primary lung abnormalities are confined to SSc-ILD, apart from anecdotal reports of obliteratorive airway disease, diffuse alveolar haemorrhage and pleural disease (not considered further). Pulmonary vascular disease and cardiac involvement in SSc are large separate topics, not covered in this review. In this overview of SSc-ILD, our knowledge of epidemiology and pathogenesis is summarised. Larger sections follow in which key clinical uncertainties are explored and management dilemmas are discussed in detail.

Epidemiology of SSc and SSc-ILD

It has been difficult to define the epidemiology of SSc-ILD with any degree of precision. In part, this reflects the fact that SSc is a rare disease (estimated prevalence 50–300/million) [1]. To
complicate matters, SSc has a clinically heterogeneous course, with major variation in the severity of SSc-ILD. As discussed later, the presence of interstitial lung disease cannot be reliably deduced from the presence or severity of respiratory symptoms. Reliance on the presence of exertional dyspnoea, in defining the prevalence of lung involvement, will result in the systematic exclusion of a large minority of SSc-ILD patients with mild interstitial disease. The spectrum of SSc-ILD ranges from limited lung involvement, which is often non-progressive, to severe disease which may progress to respiratory failure and death. In addition, the compilation of accurate epidemiological data has been seriously confounded by lack of consistency in case ascertainment, including differences in the use of tests to define pulmonary disease. Recently, some of these problems have been confronted with the construction of international collaborative databases, with the large scale compilation of clinical data. This effort has undoubtedly been facilitated by the reclassification of histological patterns of the diffuse parenchymal lung diseases [2]. The standardization of nomenclature and the criteria used to characterize histologic appearances led to an increased focus, using high resolution computed tomography (HRCT), on the presence and nature of SSc-ILD. It should be stressed that lung biopsy is seldom performed in SSc-ILD: no large historical series exists allowing the histologic definition of the prevalence of interstitial lung disease. However, the reclassification of the interstitial pneumonias led indirectly to the acceptance of a multidisciplinary clinical-radiological-pathologic correlation as the diagnostic gold standard in interstitial lung diseases. This, in turn, catalysed the integration of clinical and HRCT data in the identification of SSc-ILD, validating the diagnostic approach taken in the EUSTAR database [3], currently the most reliable source of large population outcome data in SSc. The EUSTAR database confirmed earlier reports in less definitive cohorts that SSc-ILD is now the most frequent cause of death in SSc. In the EUSTAR cohort of over 5800 patients, 35% of SSc-related deaths were directly attributable to SSc-ILD. Pulmonary arterial hypertension (PAH) was responsible for 26% of deaths. Thus, there has been a striking shift in patterns of mortality in SSc over the last 25 years. Pulmonary disease now greatly exceeds renal disease as a cause of SSc mortality, reflecting improvements in the diagnosis and management of SSc renal disease (which caused only 4% of deaths in the EUSTAR cohort).

In SSc at large, there is a female predominance, variably reported as a female:male ratio of 3:1 to 14:1, and a peak age of onset in the fourth to sixth decade [1]. In several large USA series, African American ethnicity has consistently been identified as a risk factor for SSc-ILD, with severe restrictive lung disease associated with male gender and SSc cardiac involvement [4,5]. The severity of SSc was greater in African-American and Hispanic patients than in Caucasians, and the onset of SSc tended to occur at a younger age in African-Americans [6]. However, these demographic and racial predilections for SSc cannot be extrapolated to the development of SSc-ILD which, as discussed later, is more strongly linked to the pattern of skin involvement and autoantibody status. In early autopsy studies, there was evidence of interstitial lung disease in most SSc patients [7], but this finding must be interpreted with caution in patient cohorts dominated, by definition, by advanced SSc. A more accurate characterization of the nature of SSc-ILD can be made from smaller historical series of patients undergoing diagnostic surgical biopsy (which was performed more frequently before the advent of HRCT), although severe disease tends to be under-represented in such series. In the largest series to date, reported from an SSc cohort in which surgical biopsy was performed by protocol to characterize SSc-ILD, non-specific interstitial pneumonia (NSIP) was the most prevalent histologic pattern, seen in 62 of 80 patients (78%) [8]. In the remaining patients, the most frequent patterns were usual interstitial pneumonia (UIP) (8%), end-stage lung disease (8%) and smoking-related interstitial lung disease (respiratory bronchiolitis-associated interstitial lung disease) in three cases. Mortality in this cohort was not linked to the histologic pattern but was primarily determined by the severity of physiological impairment and declines in pulmonary function tests during follow-up. Importantly, potentially reversible interstitial lung disease (cellular NSIP or smoking-related lung disease) was present in less than 25% of cases. The findings in this series are wholly compatible with subsequent HRCT findings in larger SSc-ILD cohorts, and it is now accepted that NSIP is the predominant histologic pattern in SSc-ILD. This contrasts greatly with idiopathic interstitial lung disease, in which UIP (the defining histologic pattern of idiopathic pulmonary fibrosis [IPF]) is much more prevalent than NSIP. The histologic series discussed above was highly influential in removing the performance of diagnostic surgical lung biopsy from investigative algorithms in SSc-ILD, both because of the high prevalence of NSIP and because the histologic pattern provided no additional information on the likely outcome. As discussed earlier, the advent of HRCT revolutionised the identification and characterisation of SSc-ILD. Interstitial lung disease is evident on HRCT in 55–65% of SSc patients and is present in up to 96% of patients with abnormal pulmonary function tests [9,10]. The most frequently observed HRCT appearance is a variable combination of ground-glass attenuation and fine reticulation, typical of NSIP. In the largest comparative series, containing over 200 patients with SSc-ILD and smaller “control” cohorts of biopsy proven IPF and idiopathic NSIP, HRCT appearances in SSc-ILD were, on average, identical to those in idiopathic NSIP and differed strikingly from those in IPF [11]. Taken together, historical histologic data in selected patients and HRCT findings in unselected cohorts have resulted in the accurate characterisation of SSc-ILD. The use of HRCT has

transformed the definition of SSc-ILD in large cohorts. However, it is worth stressing that the sensitivity of HRCT in identifying limited lung disease which is not necessarily clinically significant has posed the major management problem of when to initiate treatment in SSc-ILD. The delineation of the natural history of SSc-ILD in large historical cohorts [12–14], and the evaluation of HRCT data in recent series [15,16] has helped greatly with treatment decisions, as discussed later in the section on key clinical problems.

Risk factors for the development of interstitial lung disease

Several factors have been linked to the presence of interstitial lung involvement in SSC. The distinction between limited and diffuse cutaneous disease and the autoantibody profile are both influential. Genetic associations have been reported between various MHC alleles and non-MHC genes and pulmonary disease.

Patterns of cutaneous involvement in SSc

The extent of skin involvement in SSC is classified as limited cutaneous (lcSSc) or diffuse cutaneous (dcSSc) disease. In lcSSc, there is no skin involvement proximal to the elbows or knees, although the face or neck may be involved. In dcSSc, skin disease often involves the trunk, shoulder, pelvic girdles, face, and acral areas. Historically, the pattern of skin involvement was regarded as a highly useful guide as to the likelihood of SSc-ILD, but this view has been now been seriously undermined. The prevalence of SSc-ILD is higher in dcSSc than in lcSSc (53% versus 35%) [17], but the difference is prevalence is not sufficiently large to justify the integration of patterns of skin involvement in screening algorithms. Moreover, it appears increasingly likely that these observed linkages merely reflect more powerful associations between the autoantibody profile and the presence of SSc-ILD. In analyses of the EUSTAR database, 15 of the organ complications were primarily related to the autoantibody profile whereas 11 of the organ complications were more strongly associated with the pattern of skin involvement. This implies that autoantibody status is a more useful predictor of organ involvement, including the presence of lung disease.

Autoantibody profiles in SSc

Antinuclear antibodies (ANA) are present in over 90% of SSC patients. Specific ANA profiles have provided useful predictive information regarding clinical phenotypes. The mechanism of production of autoantibodies and their role in the development of the clinical phenotypes is not well understood. It is likely that MHC class II HLA molecules play an important role, as discussed later.

The topoisomerasases are a family of enzymes acting to altering the tertiary structure of DNA. Amongst six topoisomerase enzymes identified in humans, antibodies have been detected only against topoisomerase I [18]. Anti-topoisomerase I autoantibodies (ATA), also known as anti-scleroderma-70 antibodies are present in approximately 20% of SSc patients, mostly in association with dcSSc. SSc-ILD is most prevalent in ATA-positive patients, with over 85% of developing pulmonary fibrosis [19]. ATA titres have correlated with disease severity and activity, both in SSc and SSc-ILD [20,21]. By contrast, anti-centromere antibodies (ACA), found in 20–30% of patients with SSC, are associated with a low prevalence of SSc-ILD. ATA and ACA are mutually exclusive. ACA-positivity is associated with lcSSc and an increased risk of PH [4,22]. However, despite the observed linkage to PH, ACA positivity was found to predict higher survival in a multi-ethnic cohort of 250 SSc patients [23], reflecting the importance of SSc-ILD as a determinant of SSc-related mortality.

The high specificity of ATA-positivity with regard to the development of SSc-ILD presents a strong argument for including the characterization of autoantibody status in clinical algorithms for the detection of lung involvement in SSc. However, it is clear that autoantibody status alone cannot be used to determine which SSc patients should undergo screening HRCT evaluation. SSc-ILD is present in a significant minority of SSc patients with a wide variety of other autoantibodies. As 80% of SSc patients are ATA-negative, SSc-ILD is more often associated with ATA negativity, reported in 72 of 120 (60%) of SSc-ILD patients in one study [24] and supported by widespread anecdotal experience.

Genetic associations

It is generally accepted that a variety of environmental factors interact with genotypes to produce the clinical phenotypes characteristic of SSc. However, the genetic complexity of SSc has proved to be a major constraint in defining specific genetic associations. Further difficulties have included the low prevalence of SSc, its clinical heterogeneity and the likelihood that multiple genetic loci confer disease susceptibility. Evidence for a genetic predisposition includes familial cases (including twins) [25], the increased prevalence of autoantibodies and other rheumatic diseases in family members and the genetic associations with specific autoantibodies, summarised below. The most compelling data comes from a study of Choctaw Indians in southeastern Oklahoma, found to have a 10-fold increase in the prevalence of SSc [26]. Choctaw Indians with SSc tend to have diffuse cutaneous disease (dcSSc) with SSc and a prevalence of ATA positivity of more than 80%. A genome-wide screen showed that SSc in this population is associated with multiple microsatellite markers in different chromosome regions, with candidate regions including the MHC, fibrillin 1 gene (15q), the topoisomerase 1 gene (chromosome 20q) and the SPARC gene (secreted protein, acid rich in cysteine; chromosome 5q).
Genetic associations have also been observed with a number of markers implicated in the pathogenesis of SSc-ILD. CTGF has been associated with a functional polymorphism [27] and has emerged in recent genome-wide association studies and subphenotype analyses [28,29]. An association between the IL6 gene and SSc has also been reported [30]. The rs763361 single nucleotide polymorphism (SNP) in the CD226 gene (involved in the adhesion and co-stimulation of T cells) is associated with dcSSc, ATA positivity and SSc-ILD [31]. Interestingly, the same SNP has been associated with other autoimmune conditions (type 1 diabetes mellitus, multiple sclerosis, rheumatoid arthritis), suggesting a shared autoimmune susceptibility genotype [32].

A number of MHC or human leukocyte antigen-class II (HLA-class II) alleles have been associated with SSc and various SSc related autoantibodies. HLA-class II is of particular genetic interest in SSc because of its potential role in autoantibody production. It is believed that that antigen is presented by HLA-class II molecules to helper T cells, leading to activation and proliferation of an antigen-specific autoantibody response. ATA positivity is reported to be strongly linked to the carriage of the HLA-DRB1*11 and HLA-DPB1*1301 alleles [24]. Linkages between SSc-ILD and non-MHC related genes have been evaluated in several studies. In a Japanese study, SNPs in the surfactant protein B (SP-B) gene were associated with a lower risk of SSc-ILD [33]. Genetic polymorphisms reported to predispose to SSc-ILD included the IL-1α and IL-1β genes [34,35].

**Pathogenesis of SSc-ILD**

The pathogenesis of SSc-ILD involves interplay between multiple cell types [36]. It is probably unrealistic to view any single pathway as a cardinal pathogenetic pathway. At the end of the last century, it was widely accepted that in interstitial lung disease, disease was likely to originate from dysregulation of the alveolar epithelium, resident fibroblast populations (or circulating progenitor cells) or the connective tissue matrix, linked to genetic predilection and, in autoimmune lung disease, to systemic or pulmonary immunologic dysregulation. Since that time, support for the pathogenetic importance of all these candidate compartments has been compiled in a large number of studies. However, no primary pathway has emerged and it appears increasingly likely that traditional single pathway models, generally used in drug discovery, are over-simplistic models for the pathogenesis of interstitial lung disease. Current thinking is now focused on the integration of pathways, along the lines summarised below.

One of the earliest pathogenetic events is an influx of inflammatory cells into the lung interstitial and the alveolar airspaces. In a large number of interstitial lung diseases, the critical early importance of alveolar epithelial damage has been emphasised. Although less studied in SSc, it is clear that epithelial damage exists and that the severity of epithelial damage is a major determinant of the likelihood of progression of lung disease [37,38]. The importance of epithelial damage is highlighted by clinical studies of SSc-ILD patients. Rapid clearance of inhaled 99mTc-DTPA clearance and KL-6 serum levels, both markers of alveolar epithelial damage, predict progression and reflect the severity of SSc-ILD [39,40]. Further support for a role for alveolar epithelial injury comes from studies of a mouse strain that has a number of features of SSc [41,42]. The intra-tracheal instillation of mildly acidic unbuffered normal saline leads to lung injury and fibrosis, with EM studies confirming the presence of epithelial injury. In addition, in this model, the development of interstitial fibrosis was associated with attenuated type II pneumocyte proliferation (and, thus, dysregulation of an important lung repair mechanism) and persistence of a myofibroblast population after injury.

Inflammation and epithelial damage result in the activation of interstitial pulmonary fibroblasts that are resident in the connective tissue spaces of the lung and the alveolar wall [43]. Pulmonary fibroblasts are activated by a variety of pathways and mediators, including TGF-β dependent pathways [44]. These cells appear to regulate and control other cellular processes, promoting a profibrotic microenvironment in damaged lung tissue and activating and recruiting of active TGF-β ligand from lung tissue [45]. Thus, it is plausible that infection, environmental or chemical stimuli (including micro-aspiration) result in epithelial damage and inflammation and have a central role in the initiation, amplification or persistence of initial pathogenetic pathways [43,44].

Activated fibroblasts and myofibroblasts are key effector cells in pulmonary fibrosis, producing increased amounts of extracellular matrix protein. The population of activated fibroblasts and myofibroblasts has three potential sources, all potentially relevant to the development of SSc-ILD. These cells may derive from the resident interstitial fibroblasts [43], as shown by experiments on transplantation specimens which have confirmed the importance of resident progenitor cells in the lung [45]. Activated fibroblasts and myofibroblasts may also arise from circulating progenitor cells recruited to damaged lung tissue [44], as seen in animal models studies of lung injury in which a substantial proportion of fibroblasts derive from circulating progenitors [46]. Experimental work in mutant mice suggests that resident interstitial pulmonary fibroblasts plays a central role in the recruitment and/or differentiation of circulating progenitor cells in sites of lung injury [47,48]. Profibrotic mesenchymal cell populations in lung fibrosis may also arise from epithelial-mesenchymal trans-differentiation, although the pathogenetic importance and of this process is less clear.

Irrespective of the source of activated fibroblasts, the central role of the resident lung fibroblast population is strongly by the absence of lung fibrosis in experimental mouse models in...
which these cells have been targeted by genetic strategies that attenuate TGF-beta responsiveness or signalling. In this animal model, pulmonary fibrosis is almost completely attenuated following intra-tracheal bleomycin injury. In complementary experiments in the same mouse model, the use of a VEGF receptor inhibitor leads to a proliferation occlusive pulmonary vasculopathy with histological and functional similarities to SSC-associated PH [49]. Taken together, these animal model studies provide support for the concept of major lung complications occurring with appropriate triggers or co-factors.

Thus, the most plausible pathogenetic model for SSC-ILD lung involves an evolution from initial inflammation and injury to a lung microenvironment that favours fibrosis, triggered by cofactors such as infection and micro-aspiration and amplified by genetic factors. To this model must be added intrinsic differences in the pathogenetic mechanisms of SSC, and especially in SSC disease sub-types identified by hallmark autoantibodies. As discussed earlier, ATA-positive SSC patients are more likely to develop lung fibrosis. Other less prevalent antibodies associated with a higher prevalence of SSC-ILD included anti-U11/U12 or anti-Th/To [50]. The contribution of the innate and adaptive immune system to the development of SSC-ILD is less clear but studies suggest a role for both. There is evidence for the involvement of alternatively activated macrophages and restricted clonality of lung T cells [51,52], both suggesting that an underlying antigenic drive. In addition, multiplex analyses of serum cytokines are indicative of a unique profile compared to sarcoidosis-associated lung fibrosis and IPF [53].

Key questions in the clinical evaluation of SSC-ILD

What are the causes of dyspnoea in SSC-ILD?

The difficulties that may arise in interpreting respiratory symptoms in SSC, especially exertional dyspnoea, cannot be over-emphasised. Even in patients without lung involvement, systemic manifestations which profoundly influence exercise tolerance, both at a single point in time and with regard to serial change. Fatigue is common in systemic autoimmune disease and may be disabling. When severe fatigue is present, the patient may have difficulty in deconstructing the relative contributions of fatigue and loss of pulmonary reserve to loss of exercise tolerance, with the two symptoms often amalgamated as “breathlessness”. Musculoskeletal involvement is also a frequent confounding factor. Arthralgia and myalgia may give rise to major increases in the work of locomotion, resulting in severe exertional dyspnoea, even in the absence of interstitial lung disease. However, active systemic disease may lead to exercise intolerance, due either to severe anaemia or, more frequently, inactivity in day-to-day life with consequent weight gain and loss of fitness. As discussed later, exercise testing has no routine role in the evaluation of the severity of SSC-ILD. However, when major exercise intolerance is associated with systemic morbidity and appears disproportionate to the severity of lung involvement, the six-minute walk test may provide highly useful information. By reproducing exertional dyspnoea, it is sometimes obvious from observation of the patient that exercise limitation is not due to pulmonary disease, especially when there is no oxygen desaturation when dyspnoea causes cessation of the test. Difficulties in linking loss of exercise tolerance to SSC-ILD are not confined to extra-pulmonary confounding factors. Reduced exercise tolerance in SSC may also result from smoking-related lung disease, pulmonary vascular limitation (even in the absence of overt PH), sclerodermatous cardiac involvement, cardiac disease unrelated to SSC or pulmonary infection. Increasing cardiac or pulmonary vascular limitation, in particular, may simulate progression of interstitial lung disease, especially when declining exercise tolerance is the sole clinical manifestation of advancing disease. Thus, whenever progressive exercise limitation is disproportionate to the severity of interstitial lung disease, pulmonary vascular and cardiac evaluation are appropriate. Acute or sub-acute infection is an occasional cause of apparent lung involvement in SSC but is often disclosed by sputum production or systemic symptoms. However, the extra-pulmonary symptoms of infection may be suppressed by immunosuppression for systemic disease. Moreover, in treated patients with fibrotic disease, the clearance of infected secretions may be compromised by structural damage and by the inhibition of host defence mechanisms by immunosuppressive therapy.

For all these reasons, the presence and severity of exertional dyspnoea are not a reliable guide as to the presence and severity of SSC-ILD. It is not uncommon, in an individual patient, for exercise tolerance to be influenced by several of the factors discussed above. The challenge for the clinician is to deconstruct the causes of exertional dyspnoea and to focus interventions on those factors that can, realistically, be improved.

Is interstitial lung disease present?

It is now widely accepted that HRCT is the only reliable means of identifying SSC-ILD. Traditional means of identifying interstitial lung disease, including chest radiography and clinical examination, are relatively insensitive. The limitations of exertional dyspnoea as a means of identifying lung disease are discussed above. Pulmonary function tests are reliably indicative of lung involvement when there is a severe restrictive ventilator defect but are more often difficult to interpret due to the width of the normal range (80–120% of predicted). A measured forced vital capacity value of 80% in an individual patient may equally represent the absence of change or a major decline from a pre-morbid value of over 110%. Moreover, pulmonary function variables are influenced by a wide range of pulmonary and extra-pulmonary comorbidities including concurrent smoking-related emphysema, pulmonary vascular disease and extra-pulmonary
limitation [54]. Historically, it was believed that bronchoalveolar lavage (BAL) might allow the early detection of SSc-ILD before abnormalities had become apparent on imaging. However, it is now accepted that the presence of a “sub-clinical alveolitis” on BAL (i.e. a BAL lymphocytosis in the absence of other evidence of lung involvement) is not predictive of the subsequent development of SSc-ILD.

By contrast, HRCT is both sensitive and specific in the identification of SSc-ILD. The major drawback of HRCT is the frequent presence of sub-clinical abnormalities that do not necessarily progress. In a series of over 200 patients with SSc-ILD, the extent of interstitial abnormalities was trivial or very mild (involving less than 10% of the lung) in over 40% of cases [16]. Thus, it can be argued that HRCT is too sensitive to serve as a routine screening tool for SSc-ILD in unselected SSC patients. Proponents of this view reason that HRCT should be used routinely to confirm or exclude SSc-ILD only in higher risk groups (e.g. ATA-positive SSC patients) or when there is reason to suspect the presence of SSc-ILD, based on symptoms, clinical examination, chest radiography or pulmonary function abnormalities. However, others, including the author, contend that routine HRCT is warranted in SSC as normal appearances are definitive and the identification of limited interstitial abnormalities leads to an appropriate level of surveillance in those cases. Optimal screening protocols for SSc-ILD are currently being considered by an international expert group.

When is the clinical value of HRCT evaluation?

The identification of lung involvement aside, HRCT adds usefully to the clinical evaluation of SSc-ILD in a number of important respects. The spectrum of HRCT abnormalities typical of SSc-ILD is now well characterised, as discussed earlier. From time to time, SSC patients present with other forms of lung disease, including smoking-related or drug-induced interstitial lung disease, with the likely diagnosis disclosed by HRCT appearances. Prominent consolidation, admixed with fibrotic reticular abnormalities, is a frequent HRCT finding in inflammatory myopathy [55] but is very infrequent in SSC and may, thus, when present in SSC, be indicative of hitherto unsuspected overlap syndrome. As discussed later, HRCT may be invaluable in the accurate interpretation of pulmonary function abnormalities, in the setting of major comorbidities such as PH and smoking-related emphysema [54]. However, studies of the clinical utility of HRCT evaluation have mostly focused on the identification of reversible disease and, more recently, on the quantification of disease severity (discussed in the section on prognostic evaluation).

In idiopathic interstitial lung disease, extensive ground-glass attenuation on HRCT is indicative of a higher probability of reversible inflammatory cell infiltration and, thus, a greater likelihood of responsiveness to anti-inflammatory or immuno-suppressive therapy. However, early enthusiasm for the use of HRCT to guide therapy was dampened by the realisation that ground-glass is also seen on HRCT in the setting of fine intralobular fibrosis, most commonly in the setting of fibrotic NSIP. This is due to the resolution limitations of HRCT. Anatomical structures manifest on HRCT as variations in density, measured in spatial units (“voxels”). Intra-lobular fibrosis that is finer than the width of individual voxels is seen on HRCT, not as a classic fibrotic reticular abnormality, but as a diffuse increase in average density, indistinguishable from ground-glass due to inflammatory cell infiltration. The likelihood that a ground-glass pattern is irreversible increases when it is associated with admixed fine reticular abnormalities, as first described in a study of SSc-ILD [56], and when there is traction bronchiectasis due to fibrotic traction on airways [57]. However, even when these two ancillary signs are absent, prominent ground-glass attenuation is not reliably synonymous with inflammatory disease. In SSc-ILD, reversible inflammatory interstitial disease is present at surgical biopsy in less than 25% of cases [8], but ground-glass attenuation makes up, on average, at least 50% of abnormalities seen on HRCT and is usually present, even when reticular change is more extensive [11]. The limitations of HRCT in identifying reversible disease have been underlined by studies of serial CT change. When there is admixed reticulation, present in the majority of patients with SSc-ILD, partial regression of disease is seen on HRCT in only a third of patients [58] and in the longer term, ground-glass attenuation usually evolves to overt fibrotic abnormalities [9]. In a serial HRCT study of 41 SSC patients, ground-glass attenuation was seen in two thirds of cases but regressed in the next two years in only two patients and was usually resistant to treatment [59]. Thus, the widespread use of the phrase “alveolitis on CT” as synonymous with the presence of ground-glass as a marker of reversible SSc-ILD is highly inaccurate. The greater utility of HRCT, in this regard, lies in the identification of unequivocal fibrotic abnormalities, ranging from fine to coarse reticulation and, in a minority of patients, honeycomb change. When fibrotic abnormalities predominate on HRCT, the prevention of disease progression is the only realistic therapeutic goal.

Does the presence of SSc-ILD mandate therapeutic intervention?

This important question was seldom confronted in most historical series and review articles in this field. Attention tended to focus on the identification of SSc-ILD as the most malignant prognostic determinant in recent SSC cohorts. As a result, many patients with limited SSc-ILD, including those with sub-clinical HRCT abnormalities, were subjected to aggressive intervention and in many cases it is clear that treatment caused more harm than good. It is now widely accepted that therapeutic intervention is not appropriate in asymptomatic SSC patients when disease is limited on HRCT and pulmonary function abnormalities are absent or trivial. This profile can be viewed as
“clinically insignificant disease”’. When doubt exists on this point, it may be appropriate to allay patient and clinician anxieties with the performance of a maximal exercise test. If the exercise test is normal, judged by a high maximum oxygen consumption and the absence of oxygen desaturation or widening of the alveolar-arterial oxygen gradient, it can be concluded with confidence that limited HRCT abnormalities are indeed sub-clinical.

Even when SSc-ILD is not sub-clinical, immediate intervention is not necessarily warranted. Ideally, treatment should be instituted when there is major pulmonary inflammation or fibrotic disease is progressive. However, meticulous observation is appropriate in intrinsically stable SSc-ILD. Thus, optimal management is utterly dependent on accurate prognostic evaluation, discussed later in this review.

**How should pulmonary function tests be used to stage the severity of SSc-ILD?**

It has long been accepted that in interstitial lung disease, pulmonary function tests (PFT) reflect the severity of the underlying histopathologic process more accurately than symptoms or chest radiographic findings [60]. In SSc, PFT have been strongly predictive of outcome [61,62], with a marked increase in mortality in patients with carbon-monoxide diffusing capacity (DLco) levels below 40% of predicted [62], reflecting the fact that measures of gas transfer are reduced in both pulmonary fibrosis and pulmonary vascular disease. Severe restriction (e.g. a reduction in forced vital capacity [FVC] below 60%) has also been linked to a striking increase in mortality [4]. The prognostic value of baseline PFT is equally high in patients with SSc-ILD, with increasing impairment of all resting and exercise variables associated with increased mortality [12]. In general, pulmonary fibrosis is characterised by a restrictive pulmonary defect (reduced total lung capacity and FVC; increased FEV1/FVC ratio) and a reduction in DLco [63], which is usually significantly greater (expressed as a percentage of normal predicted values) than the fall in FVC. In SSc-ILD, arterial oxygen levels are usually well preserved (in the absence of PH) until interstitial lung disease is advanced.

Because a great many resting PFT can be measured routinely, a number of studies have been performed in interstitial lung disease to determine which variables correlate most strongly with the global morphological extent of disease. In SSc-ILD, DLco levels reflect the extent of disease on HRCT more accurately than lung volumes, which correlate surprisingly poorly with the morphologic extent of disease [64]. The greater accuracy of DLco levels in this regard reflects a more complete capture of the functional impact of morphologic abnormalities. The uptake of carbon-monoxide is dependent equally on the inspired volume and the blood volume within ventilated lung. The DLco level, a mathematical product of measured alveolar volume (VA) and the measured blood volume, as judged by carbon-monoxide uptake per litre of VA (Kco), thus, captures fibrotic ablation of both alveolar airspaces and pulmonary blood vessels. The phenomenon of “signal-noise ratio” is also an important consideration. DLco levels in pulmonary fibrosis are usually much lower than lung volumes, due to the impact of the fibrotic ablation of the pulmonary vasculature. In a study of placebo-controlled evaluation of oral cyclophosphamide in SSc-ILD, mean DLco levels were less than 50% of predicted, whereas mean FVC values approximated 70% [15]. The wide range of normal values (80–120% of predicted) is an important source of “noise” for both variables but has a greater confounding effect on FVC levels which often only mildly reduced.

The severity of PFT impairment has a major bearing on decisions as to whether treatment should be introduced in SSc-ILD. Immediate intervention is almost always warranted in functionally severe disease for two reasons:

- disease progression in SSc-ILD, although occasionally rapid, is more often insidious and, thus, severe disease is usually a consequence of prolonged or repeated progression, with a high likelihood of continued deterioration if nothing is done to change the natural course of disease;
- when disease is severe, the patient is often close to their respiratory reserve and failure to prevent further disease progression may lead to major chronic disability.

By contrast, when SSc-ILD is mild at first evaluation, a less progressive natural course is plausible and there is a realistic possibility of intrinsic long-term stability. Furthermore, when pulmonary function impairment is mild, indicating a good respiratory reserve, the clinician has the luxury of knowing that with meticulous observation, continued insidious progression can be identified and treated long before disease becomes severe. However, although treatment decisions tend to be easy to make when disease is overtly severe or obviously very limited, a large proportion of SSc-ILD patients present with a level of functional impairment that is intermediate between these severity poles. Based upon the PFT-HRCT observed in fibrotic interstitial lung disease in general, and in SSc-ILD in particular [63], it appears logical that DLco levels should be the cardinal severity variable used to guide decisions on treatment. It has been argued that DLco levels below 60% of predicted should reduce the threshold for treatment [65]. However, no single severity threshold applies reliably to all patients. As discussed in greater detail in the section on prognostic evaluation, the threshold for intervention is reduced also by evidence of recent disease progression [65] and a short duration of systemic disease [4,66]. Thus, even when DLco levels are as low as 50% of predicted, a policy of observation without immediate intervention can be defended in carefully selected patients with long standing SSc-ILD, especially when there is evidence of stability on serial PFT monitoring.

It should also be emphasised that no single severity variable is intrinsically highly reliable. DLco levels are confounded by the
presence of disproportionate PH or smoking-related lung damage. FVC reduction is usually specific to interstitial lung disease (as extra-pulmonic restriction due to pleural disease, respiratory muscle weakness or extensive thoracic cutaneous disease is rare in SSc-ILD). Severe restriction is reliably predictive of extensive SSc-ILD. However, FVC levels are less sensitive than DLco levels and, as discussed earlier, more often confounded by the wide normal range. Thus, the evaluation of the severity of SSc-ILD should, in essence, be multidisciplinary with the integration of PFT, symptoms and HRCT findings. Although formal HRCT scoring of the extent of disease extent is seldom practicable in routine practice, a rapid evaluation of CT extent is often invaluable, to put PFTs and symptoms into perspective. For example, in symptomatic SSc-ILD patients with extensive disease evident on HRCT, a moderate reduction in DLco of 60–70% of predicted is likely to represent a striking fall from a high pre-morbid value. Thus, functional and morphological severity should be reconciled in order to improve the accuracy of treatment decisions. In SSc-ILD, arterial blood gases tend to be well preserved (in the absence of PH) until interstitial lung disease becomes severe. In a comparison between SSc-ILD and IPF, FVC and DLco levels did not differ between the two diseases once the extent of disease on HRCT had been taken into account [67]. However, arterial oxygen levels at rest and on maximal exercise testing were substantially higher in SSc-ILD and the authors speculated that finding this might reflect shunting through new vessel formation in IPF, recognised as a pathogenetic feature of that disease [68]. Thus, hypoxia which is disproportionate to the severity of SSc-ILD should prompt the clinician to exclude PH. Neither maximal exercise testing nor the six-minute walk test has a routine role in the evaluation of SSc-ILD. Both forms of exercise testing may have added value in the occasional difficult problem of the patient with disproportionate dyspnoea, not explained by the apparent severity of pulmonary disease (as judged by resting pulmonary function tests and findings on HRCT). Alternatively, abnormal gas exchange on exercise may inform the clinician that disease severity has been underestimated by HRCT and resting PFT. It is essential that a significant respiratory work load be achieved, with an oxygen consumption of over 50% of predicted; premature cessation of exercise due to lack of fitness or musculoskeletal disease may result in failure to disclose important abnormalities of gas exchange. Finally, disproportionate exercise-induced hypoxia (especially when seen on sub-maximal testing, as in the six-minute walk test) may disclose that pulmonary vascular involvement is significant.

What is the role of ancillary tests in the evaluation of SSc-ILD?

Ancillary tests used historically in the evaluation of SSc-ILD have included surgical biopsy (discussed earlier), bronchoalveolar lavage (BAL) and the measurement of lung clearance of inhaled 99mTc-DTPA (technetium-radiolabelled diethylene triamine pentacetate). None of these tests is now recommended in the routine evaluation of SSc-ILD. BAL may reveal evidence of alveolar inflammation in SSc before the onset of pulmonary symptoms or imaging abnormalities [69]. For many years, BAL was performed routinely in the initial evaluation of SSc-ILD, based on reports that the presence of a neutrophil alveolitis might be indicative of more progressive disease [8,70,71]. However, it is now known that a BAL neutrophilia can be expected when HRCT abnormalities are extensive and fibrotic and is likely to be merely a marker of more extensive disease, rather than an independent determinant of progressive disease [72–74]. Thus, BAL findings should not be used to determine whether treatment should be started, a finding underlined by the widespread observation that many SSc-ILD patients with normal BAL findings have progressive disease.

The rapidity of clearance of inhaled 99mTc-DTPA is a marker of increased alveolar cell permeability, with abnormally rapid clearance indicative of alveolar epithelial damage. Rapid DTPA clearance in SSc-ILD is associated with a worse outcome (as judged by a shorter time to decline in FVC, before and after adjustment for disease severity) [40]. However, this test is not widely available, does not provide useful information in current or recent smokers and the associated radiation burden limits its value in routine practice.

What factors are predictive of disease progression?

The frequent clinical problem of the presence of sub-clinical or limited SSc-ILD has been a recurrent theme in this review. Perhaps the most difficult clinical dilemma in the management of SSc-ILD is the need to introduce treatment when disease is progressive but to avoid side-effects from unnecessary treatment when SSc-ILD is intrinsically stable. No consistently reliable means of identifying progressive disease currently exists but it is now widely accepted that three factors should considered in decisions to institute therapy:

- based on the data of Steen and accumulated clinical experience, SSc-ILD is more likely to progress early in the course of systemic disease. In a large cohort, SSc-ILD progressed much more frequently in the first four years of systemic disease, and especially in the first two years and in a small subset of patients, in whom the cutaneous manifestations of SSc were preceded by the onset of lung disease [4,66];
- the importance of quantifying the severity of SSc-ILD has already been discussed in the section on pulmonary function tests. Prompted by the need to integrate HRCT findings and PFTs, Goh et al. evaluated the prognostic value of HRCT and FVC severity thresholds [16]. The most accurate prognostic threshold, examined against subsequent disease progression
and mortality, was an HRCT disease extent of 20% of the total lung volume. An FVC threshold of 70% of predicted also provided useful prognostic information, whereas no single optimal DLco threshold could be identified. From these data, a staging system for SSC-ILD was developed, based on rapid HRCT evaluation. When disease extent was obviously less than, or obviously more than, 20% of the total lung volume, lung disease was categorised as “mild” or “extensive” respectively. In approximately one third of cases, this judgement was difficult to make and the FVC threshold of 70% was used instead to distinguish between mild and extensive disease. The predictive value of this staging system was subsequently confirmed [75]. Furthermore, similar HRCT and FVC thresholds were found to be predictive of likely treatment effects in the Scleroderma Lung Study of oral cyclophosphamide in SSC-ILD [15], with treatment benefits largely confined to patients with more severe disease. Taken together, these studies underline the importance of integrating HRCT observations and FVC estimation, in identifying patients who require treatment. Importantly, with HRCT having a central role in staging, FVC thresholds appear to be more discriminatory than DLco thresholds in prognostic evaluation, even though DLco levels correlate more strongly with the extent of disease on HRCT;

• finally, it is universally accepted that evidence of recent disease progression, as judged by serial PFT tends, is, in itself, an indication for therapy, although it should be acknowledged that the prognostic value of observed disease progression, well established in IPF, has yet to be definitively evaluated in SSC-ILD.

Treatment decisions require a case by case evaluation, taking into account the views of the patient. Even following careful prognostic evaluation, decisions on the introduction of therapy are often a close call. In such cases, patient preferences often result in an initial decision to observe closely, with follow-up evaluation at three to six monthly intervals (including repetition of PFTs) and immediate intervention in the event of disease progression. An accurate biomarker, identifying SSC-ILD patients at a higher risk of progression would undoubtedly improve the accuracy of treatment decisions. At present, no such biomarker has been validated but preliminary data indicate that increased serum levels of two lung glycoproteins, KL-6 and SP-D [39,76–78] and IL6 levels [79] may provide added prognostic value.

What is the optimal approach to monitoring?

The detection of change in the severity of SSC-ILD is central to accurate management. Major progression of disease is characterised by worsening exertional dyspnoea, decline in pulmonary function variables and increases in disease extent, as judged by chest radiography or HRCT. However, no single method of detecting change in disease severity is uniformly reliable, especially when progression is insidious.

As discussed earlier, exertional dyspnoea is highly multi-factorial in SSC. Changes in exercise tolerance may result from fluctuations in systemic disease activity, especially in patients with morbidity from musculoskeletal involvement, and can also reflect loss of fitness, cardiac involvement, worsening of pulmonary hypertension or lower respiratory tract infection. The chest radiograph is essentially a blunt instrument in the identification of change. Serial pulmonary function tests are the cornerstone of routine monitoring but the limitations of the pulmonary function laboratory need to be constantly kept in mind. Even in laboratories with optimal quality assurance and quality control, measurement variation is an important consideration. Changes in FVC of less than 10% from baseline values and changes in DLco of less than 15% are often ascribable to measurement variation or sub-maximal effort. Furthermore, larger changes may reflect infection and isolated declines in DLco, although sometimes occurring in interstitial lung disease, may represent worsening pulmonary vasculopathy. Optimal clinical monitoring differs from usual practice in therapeutic trials, in that no single variable can be viewed as equivalent to a primary end-point. The process of detecting change is essentially multidisciplinary, requiring the integration of symptomatic, pulmonary function and imaging variables. For example, although DLco change is not specific to the lung interstitium, a downward trend in DLco values (although not necessarily to the “significant” threshold of 15%) is expected in progressive SSC-ILD. Thus, FVC decline, even when greater than 10% from baseline values, should be viewed with scepticism when DLco values are entirely stable. For this reason, FVC and DLco levels should both be routinely monitored and progression should be strongly suspected when there is concordant change, even when changes in neither variable reach “significance” (e.g. an 8% reduction in FVC and a 13% reduction in DLco). In this context, worsening exertional dyspnoea is an important validation of disease progression.

However, in insidious progression, symptomatic change is not necessarily present and in other cases, there is discordance between symptomatic and pulmonary function tests or uncertainty whether there is progression of SSC-ILD, worsening pulmonary vasculopathy or infection. Serial HRCT is not recommended in routine monitoring due to radiation constraints but may be invaluable when clinically significant progression of SSC-ILD is suspected and other serial variables are inconclusive. Progression of interstitial lung disease is not always clearly evident on HRCT, but obvious increases in disease extent greatly reduce clinical uncertainty. An important caveat is that HRCT is sometimes too sensitive: very minor change is sometimes present in a single HRCT section and should be regarded with caution. With currently available technology, change in disease extent on HRCT can only be evaluated subjectively. Recent findings in SSC-ILD suggest strongly that automated methods are more sensitive and accurate in the
identification of morphologic change [80] and may allow the use of serial HRCT as an important end-point in therapeutic trials. However, this use of HRCT is unlikely to be applicable to routine clinical monitoring in the near future. In early monitoring, repetition of FVC and DLco at four monthly intervals is appropriate. In disease which has been stable for longer than a year, it is reasonable to perform pulmonary function tests less frequently, although it should be understood that a formal monitoring algorithm has yet to be validated. Unless SSC-ILD is trivial in extent, annual monitoring should continue, even in stable disease, with earlier evaluation in the event of symptomatic change.

Management

**Current treatment approaches**

As in fibrotic lung disease in general, historical regimens were based on a disease model in which inflammation was believed to precede and lead to fibrosis. Corticosteroid therapy, often given at low doses in combination with a “second-line” immunosuppressive agent, was the empirical approach for most clinicians, when confronted with severe or progressive SSC-ILD. To a certain extent, management was driven by the lack of alternative agents such as anti-fibrotic drugs. In lung disease associated with connective tissue disease, it could at least be argued that immunomodulation provided an appropriate strategy for systemic disease activity and was justified in lung disease by the concept of pathogenetic pathways common to all disease sites.

The apparent logic of unifying treatment approaches for systemic and lung disease was never likely to be challenged by accumulated anecdotal experience. Lung disease in connective tissue disease, especially SSC-ILD, has a very low prevalence and for this reason, treatment strategies were largely put in place by experience at referral centres. However, although treatment responses, as judged by disease regression, were rapidly apparent in a minority of cases, the larger goal of preventing or slowing progression of irreversible fibrotic disease could not be formally addressed. No single referral population was sufficiently large to power controlled treatment evaluation, with follow-up sufficiently lengthy to establish that stabilisation was due to treatment, as opposed to a natural history of reduction in disease activity.

Cyclophosphamide was the therapy to receive the most attention, with a series of case reports and uncontrolled case series demonstrating apparent showing improvements in key pulmonary function variables in some patients. Regression of disease was seen frequently in retrospective reports and was the initial focus of attention although, in the largest case series, FVC levels increased by 4% in 39 patients receiving cyclophosphamide but fell by 7% in 30 untreated patients [81]. Based on the emphasis on reversing disease, the concept that reversibility “alveolitis” was synonymous with ground-glass attenuation on HRCT and a high BAL inflammatory cell content became embedded in clinical thinking and was a key influence on enrolment criteria in the scleroderma lung study (SLS) trial [15]. To this day, reference continues to be made to “alveolitis on HRCT” and “alveolitis on BAL” although, as discussed earlier, it is now abundantly clear that reversible disease is not reliably identified by either test. In retrospect, it appears likely that open cyclophosphamide therapy was first used selectively in SSC-ILD patients with more rapidly progressive disease, with a higher prevalence of major inflammation.

However, disease regression was not consistently observed, even with encouraging early pilot data. In a meta-analysis of the effects of cyclophosphamide on pulmonary function in subsequent randomised controlled trials and observational prospective cohort studies, there was no overall improvement with treatment [82]. This conclusion was reinforced by a recent meta-analysis of 13 studies in which stabilisation of FVC, but not DLco was observed, but FVC improvement was not apparent [83]. Thus, it became increasingly clear that the larger benefit of cyclophosphamide therapy lay in preventing or slowing disease progression.

This overview of the realistic strategic goal in SSC-ILD management – the prevention of disease progression – was widely appreciated only following the post-millennial performance of multicentre treatment studies in SSC-ILD. Placebo-controlled multicentre trials of oral cyclophosphamide [15], intravenous cyclophosphamide [84] and bosentan [85] represented a long overdue departure from anecdotal historical practice. In the keynote, SLS evaluation of the efficacy of oral cyclophosphamide, statistically significant placebo-controlled treatment benefits at one year were seen on FVC levels, dyspnoea scores, the severity of skin thickening and quality of life [15]. Parallel benefits were observed on lung HRCT variables in a subsequent analysis [86]. In a parallel UK placebo-controlled trial of monthly intravenous cyclophosphamide for six months, followed by oral azathioprine, the FVC benefits were identical in amplitude to those in the SLS trial, although not statistically significant ($P = 0.08$) due to the cohort size (45 patients) [84]. When considered together, findings from these two controlled evaluations prompted EULAR to endorse the use of cyclophosphamide as a suitable therapy in SSC-ILD [87].

The EULAR statement did not convince all clinicians that the benefit to risk ratio of cyclophosphamide therapy was robust. In both trials, active treatment was associated with a relative treatment benefit, against placebo data, of less than 5% of baseline values and only 3–4% of predicted normal FVC levels. This small gain in FVC came at a price of a significant increased prevalence of adverse events in the SLS trial, although not in the UK trial. It was immediately obvious that cyclophosphamide should not be used indiscriminately in all patients with SSC-ILD. However, it also appeared very likely that the patients with the
most to gain were seriously under-represented in both studies. In the SLS trial, post hoc sub-analyses showed that treatment benefits on FVC varied with the extent of pulmonary fibrosis on HRCT [15]. When disease was limited in extent, in approximately half of cases, no treatment effect was apparent. By contrast, in patients with evidence of extensive pulmonary fibrosis, average FVC benefits exceeded 10%. In a nutshell, these findings highlighted the major drawback of placebo-controlled evaluation, despite the widespread view that this study design is essential. If an evaluated treatment is also available as open therapy, as in the case of cyclophosphamide, patients are more likely to accept the possibility of receiving placebo when lung disease is not overtly progressive or severe. We know with certainty that this crucial limitation applied to the SLS cohort: after trial completion, less than 15% of patients were prescribed open therapy upon returning to their primary physicians for routine follow-up [88].

The prevailing current view is that initial immunomodulation, usually with cyclophosphamide, is appropriate when SSC-ILD is extensive or overtly progressive, with the side effect profile justified by the need to stabilise disease. The staging classification of Goh et al. [16] is used empirically by some to rationalise which patients should be treated. In this regard, a note of caution is appropriate. Patients with “extensive disease” have a relatively poor outcome and should usually be treated. However, many patients with “mild disease” should also be treated in order to prevent progression to “extensive disease” and this applies especially to those with recent onset or overtly progressive disease and also to patients with a disease extent on HRCT that lies close to the “extensive disease” threshold. It is increasingly common practice to use intravenous rather than oral cyclophosphamide as induction therapy as the former is much less toxic, at least judging from experience in the treatment of vasculitis [89]. Again, a note of caution should be sounded: no formal trial exists establishing that intravenous and oral cyclophosphamide are equally efficacious. It should be strictly understood that the SLS and UK cyclophosphamide trials provide data on only the first year of therapy. In neither study was optimal long-term management addressed. The importance of this question was highlighted by crucial follow-up data published by the SLS group, following the formal SLS trial period [88]. Based on lung function trends after treatment cessation, comparing the active and placebo arms, it appears that the benefits of cyclophosphamide therapy had been entirely lost within 12 months, with more rapid progression evident in the active treatment arm. It is routine empirical practice, following initial cyclophosphamide therapy for 6–12 months, to introduce maintenance therapy with alternative oral immunosuppressive agents, usually given with low-dose corticosteroids. It need hardly be pointed out that no controlled data exist to validate this management algorithm.

For most, azathioprine was the first choice maintenance immunosuppressive treatment in SSc-ILD, although methotrexate was used by some clinicians. In recent years, mycophenolate mofetil (MMF) has been used increasingly as it is perceived as having lower toxicity than other agents and may have greater efficacy, although this is less clear. Retrospective analyses have documented acceptable tolerance with MMF, with 95% of SSc-ILD patients able to remain on treatment in the long term [90], a substantially higher figure than reported with the use of azathioprine or methotrexate. Accumulated clinical experience was recently buttressed by a retrospective report of open MMF therapy in over 100 patients with interstitial lung disease associated with connective tissue disease, including many with SSc-ILD [91]. MMF was well tolerated and on average, lung disease did not progress, judging from serial lung function trends, whereas disease progression was evident before the introduction of MMF. At the time of writing, the USA SLS group has completed recruitment of an important trial in which the efficacy and tolerability of mycophenolate mofetil and oral cyclophosphamide are compared. The findings are likely to be highly influential in clinical practice: the relative efficacy of the two agents is uncertain but it can confidently be anticipated that MMF will be better tolerated.

Given the paucity of controlled treatment data, clinicians can justify a flexible approach to management in SSc-ILD. The decision on whether to introduce therapy is often a terribly close call and in such cases, it is appropriate for individual patient values to be the key management determinant. It is important that if the patient chooses to defer treatment for the time being, meticulous follow-up is instituted with the stated intention that the urgent institution of treatment should be considered if further disease progression is evident. A similarly flexible approach is often appropriate when it is agreed that treatment is necessary for progressive disease that is clinically significant but not severe. In this context, not all SSc-ILD patients require cyclophosphamide therapy. Many clinicians prefer to introduce MMF at the outset, usually in combination with low dose oral corticosteroid therapy. Often, there are separate treatment indications for systemic and pulmonary disease, with a need for pulmonologists and rheumatologists to negotiate an optimal regimen. By their very nature, such decisions cannot be made from an evidence-base but rely upon logic, common sense, accumulated clinical experience and detailed discussion with the patient.

Flexibility is necessary to achieve optimal management in individual SSc-ILD patients but does not extend to the use of corticosteroids. Many view high dose corticosteroids as absolutely contraindicated in SSC. The association between renal crisis and prednisolone doses in excess of 15 mg daily is well documented [92,93]. Renal crisis leads to death or chronic renal dialysis in at least 50% of cases and is also associated with diffuse cutaneous scleroderma and the development of limb flexure contractures (as a marker of especially severe systemic
disease) [93]. It can be argued that, at least in part, the association between high dose corticosteroid therapy and renal crisis reflects the fact that both were associated historically with severe systemic disease and are linked for that reason. However, there is sufficient anecdotal experience of renal crisis being triggered by large steroid doses, in the absence of the other two risk factors detailed above, to suggest that prednisolone doses in excess of 15 mg daily should be avoided in SSC-ILD. It should also be acknowledged that the evidence-base for using low dose corticosteroid therapy in combination with immunosuppressive therapy in SSC-ILD is non-existent. As in so many other management aspects, combination therapy tends to be used because it is conceptually attractive: based on the hope of beneficial synergy and a lesser need for aggressive immunosuppressive regimens.

Future developments

Currently, the management of SSC-ILD is largely confined to immunomodulation. Two more recent developments offer promise to carefully selected patients. Bone marrow transplantation has been evaluated in small groups of patients with severe SSC, and this includes some patients with severe SSC-ILD [94,95]. This approach is analogous to “rebooting a computer” – aberrant immunological pathways are “deleted” in the hope that they will not recur following transplantation. Currently, this treatment is not practicable in most patients and is unlikely to become standard therapy in SSC-ILD: significant pulmonary function improvements have been seen in individual patients but this does not appear to occur consistently and it is not yet clear that in severe SSC-ILD, the net mortality benefit justifies the intervention. However, this question remains open.

Biological therapies have more immediate promise and this applies especially to the use of Rituximab. The first evidence of benefit came from pilot data in a handful of anti-topoisomerase positive SSC-ILD patients, compared to a small number of SSC-ILD patients receiving conventional therapies. With Rituximab therapy, there were striking relative improvements in pulmonary function data initially [96] and further improvements were seen at two years [97]. It should be understood that treatment benefits in SSC-ILD are less well documented than in lung disease associated with inflammatory myopathies. Uncontrolled treatment effects were reported in polymyositis lung [98] and, more strikingly, in a small group of patients with connective tissue disease and life-threatening lung disease [99]. In a recent retrospective study, Rituximab treatment was associated with disease stabilisation, following failure of intensive standard immunosuppression, in a number of interstitial lung diseases (excluding IPF), including a handful of patients with SSC-ILD [100]. Currently, empirical Rituximab therapy can be justified as a last resort in severe SSC-ILD progressing despite standard therapy. However, although it appears likely that Rituximab might have an important role earlier in the course of SSC-ILD, controlled data are urgently required. It is not yet known whether benefits, if any, in SSC-ILD will be confined to anti-topoisomerase positive patients. A UK comparison of cyclophosphamide and Rituximab as induction therapy in patients with SSC-ILD or lung disease associated with inflammatory myopathy is about to start recruitment.

Future interest will undoubtedly focus on anti-fibrotic agents, especially therapies shown to have treatment benefits in IPF (the most relentlessly progressive of the fibrotic interstitial lung diseases). A multicentre placebo-controlled trial of bosentan, studied for its putative anti-fibrotic effects, was definitively negative in SSC-ILD [85]. Other anti-fibrotic agents have not been evaluated in SSC-ILD. Agents with treatment effects in IPF include pirfenidone [101,102] and nintedanib [103]. Both drugs are highly pleiotropic and in the case of pirfenidone, the primary effect remains entirely uncertain, despite intensive investigation over the last decade. The pleiotropic nature of both interventions is attractive when evaluation in SSC-ILD is considered, as pathogenetic mechanisms common to IPF and other fibrotic lung diseases are likely to be targeted.

Before further trials of novel agents are developed in SSC-ILD, it is essential to reach consensus on which patients should be recruited and what end-points should be used. An expert group has advocated a policy of “cohort enrichment”, in which SSC-ILD patients at greater risk of progression (based on disease severity, a short duration of systemic disease and/or continued observed progression) are selectively enrolled [104]. The lack of sensitivity of current end-points is also a very major concern, although less of an issue in patients at high risk of progression. It is universally accepted that serial FVC is the least flawed of our current flawed primary end-points but there is a need to develop a composite primary end-point, in which the integration of FVC trends, symptomatic change and serial HRCT data (when necessary) mirrors the most accurate evaluation of disease progression in clinical practice. This approach will represent something of a “culture shift” from current trial methodology, depending as it does on changes in single primary variables. However, the pool of SSC-ILD patients suitable for clinical trials is not large. The perceived benefits of novel agents in relatively small trial cohorts (compared to those in more prevalent diseases) are likely to be critically dependent on a more accurate definition of disease progression than can be achieved with the use of change in FVC.

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References


[48] Hoyles RK, Derrett-Smith EC, Khan K et al. An essential role for resident fibroblasts in experimental lung fibrosis is defined by lineage-specific deletion of high-affinity type II transforming growth factor receptor. Am J Respir Crit Care Med 2011;183:249-61.


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