Pulmonary manifestations in scleroderma: a review

Genga E, Oyoo GO

Department of Clinical Medicine and Therapeutics, College of Health Sciences, University of Nairobi, Kenya

Corresponding author:
Dr GO Oyoo. Email: geomondi@hotmail.com

Abstract

Background: Scleroderma is a chronic multisystem autoimmune disease of unknown aetiology. Scleroderma is characterized by widespread obliterative vasculopathy of small arteries and is associated with varying degrees of tissue fibrosis and multiple organ involvement. Pulmonary disease is an important component of SSc. It is estimated that 80% of patients with SSc have some evidence of pulmonary disease. Systemic sclerosis has the poorest prognosis amongst rheumatology diseases with the highest case-specific mortality of any of the autoimmune rheumatic diseases as well as causing major morbidity.

Objective: This article will review pathogenesis, diagnosis and management of pulmonary disease in scleroderma.

Data source: Literature review of relevant published literature from both Africa and the rest of the world.

Data synthesis: The pathogenesis of lung disease in scleroderma involves a variety of pathways, including immunological/inflammatory activation and vascular injury. The primary cytokines responsible for the disease are unknown but it is postulated that it involves a complex interplay between inflammatory, B lymphocyte antibody production, oxidative stress and fibrotic pathways. This leads to the activation of lung fibroblasts by inflammatory and fibrotic mediators. Lung fibroblasts play a central role in the deposition of excess intracellular matrix. This inflammatory response leads to fibrosis and occurs in the setting of vascular derangements. The most common symptoms are dry cough and dyspnea on exertion. The high morbidity and mortality seen in SSc is generally attributed to the two major pulmonary manifestations of the disease: interstitial pulmonary fibrosis, or interstitial lung disease, and pulmonary arterial hypertension. Exertional dyspnea and dry cough are the most common presenting symptoms in patients with SSc who develop pulmonary involvement Algorithm of diagnostic procedures in these patients does not differ considerably from the procedures of any other interstitial lung disease. At the current time, cyclophosphamide remains the best studied therapeutic agent although alternatives are actively being evaluated. The pathogenesis of pulmonary disease in scleroderma is still an enigma and is being actively researched. This will advance our understanding of the disease and ability to care for these patients.

Conclusion: Pulmonary complications are common in SSc and are the leading causes of death. Careful evaluation by the clinician is warranted to detect the presence of an ILD and to select patients appropriately for consideration of therapy. It is a major clinical challenge largely due to the enigma of the disease pathology as well as limited therapeutic options available. This is compounded by the perceived lack of evidence for clinical effectiveness of those treatments that are currently in use. Clinical trials are underway and offer hope for novel approaches to this mysterious and often devastating manifestation of scleroderma.

Introduction

Scleroderma is a chronic systemic disease of unknown aetiology. It affects around 15 persons in one million inhabitants in all parts of the world. The most affected are frequently women aged between 40–60 years. Previously reported incidence and prevalence estimates vary greatly according to geographic location and methods of case ascertainment. Classification criteria were not developed until 1980 when the American Rheumatism Association (now the American College of Rheumatology, ACR) proposed criteria to distinguish SSc from other connective tissue diseases[1]. The exact prevalence in Africa is not known. Scleroderma can affect many organs in the body, including the lungs, although not everyone will experience the symptoms of lung disease. Scleroderma is divided into limited and diffuse based on the extent of skin involvement. Limited cutaneous involves the forearms, hands, legs, feet and face. Diffuse cutaneous can involve any body

area. Both will involve internal organs, differentiating them from the localized form. The last major category, Sine, is rare and involves only internal organs, sparing the skin. The major mortality and much of the morbidity of scleroderma arises through the development of specific complications of the disease including organ based complications such as cardiopulmonary, renal or gastrointestinal manifestations. The frequency and diverse nature of these complications makes systematic assessment and long term follow up essential to good management of scleroderma. Pulmonary involvement occurs in at least two thirds of systemic sclerosis patients and about 10-15% of them will develop severe lung disease during the course of their illness. Pulmonary disease has surpassed renal disease and is now the leading cause of death amongst patients with scleroderma. The estimated mortality of pulmonary disease from all causes is said to be 33%[2]. This makes pulmonary disease second only to esophageal disease as the most commonly seen visceral component. Moreover, pulmonary involvement has a poorer prognosis. The pulmonary complications are Interstitial Lung Disease (ILD) or pulmonary fibrosis and Pulmonary Arterial Hypertension (PAH). Median survival in sclerodermal patients with pulmonary hypertension ranges between 1 and 3 years[4]. In subjects with severe progressive pulmonary fibrosis the mean survival is less than 3 years[5]. PAH can occur as an isolated form, in the absence of significant interstitial lung involvement, in approximately 12-16% of patients, and is associated with a long history of Raynaud's phenomenon, limited cutaneous involvement and anticentromere antibody positivity[6]. Compared to the idiopathic form of pulmonary hypertension (IPAH), where an actively proliferating plexiform lesion is found in the pulmonary arteriolar walls, a more fibrotic, concentric-obliterative lesion predominates in SSc-associated PAH. Apart from the common complications of pulmonary vasculopathy and ILD, other less frequent pulmonary complications have been reported in SSc. Pleural effusions, perhaps related to serositis and spontaneous pneumothorax have been in the context of ILD[7, 8]. Several large studies have found a high prevalence of lung cancer in SSc patients[9]. These patients are typically female with underlying ILD. The histological types of malignancy include bronchoalveolar carcinomas and adenocarcinomas, tumors less likely to be associated with a history of cigarette smoking[10]. Several studies showed that the disease modifying drug, cyclophosphamide, can reduce the progression of scleroderma ILD in patients with early symptomatic disease with stabilization and also improve the extent of skin indurations. Pulmonary vasodilators have been shown to improve exercise tolerance and slow the rate of clinical deterioration in PAH. Improved survival in scleroderma is associated with better ascertainment of internal organ disease[11].

Pathogenesis

The pathogenesis of SSc-ILD involves a variety of abnormalities, including immunological/inflammatory activation and vascular injury. The primary cytokines responsible for the disease are unknown but it is thought that it involves a complex interplay between inflammatory cytokines, B lymphocyte antibody production, oxidative stress and fibrotic pathways leading to the deposition of excess intracellular matrix[12]. Lung fibroblasts play a central role as they are activated and produce extracellular matrix as well as many of the inflammatory and fibrotic mediators. This inflammatory response leads to fibrosis and occurs in the setting of vascular derangements[13]. Although the precise sequence of events is unclear, chronic inflammation, possibly in response to an unknown injury, is believed to play a significant role in the fibrotic process. This contrasts with idiopathic pulmonary fibrosis, where the hypothesis of inflammation preceding fibrosis has been largely abandoned, not least because anti-inflammatory and immunosuppressive agents are largely ineffective[14]. Humoral and immune cell abnormalities are found in SSc, including the presence of autoantibodies specific to the disease, chronic mononuclear cell infiltration of affected tissues, and dysregulation of lymphokine and growth factor production[15, 16]. In SSc-ILD, studies on bronchoalveolar lavage have shown a gene expression signature consistent with increased expression of chemokine and chemokine receptor genes involved in the recruitment of T cells and chronic macrophage activation, with CD8+ T cells mainly expressing pro-fibrotic Th2 cytokines IL-4 and IL-5. Proteomic analysis confirms the predominant Th2 cytokine profile in SSc bronchoalveolar lavage fluid[17].Patients with systemic sclerosis express a variety of disease-specific autoantibodies, mostly mutually exclusive and associated with different subsets of the disease. The autoantibodies classically associated with SSc and most frequently found are anti-topoisomerase (ATA, also known as Scl-70), anti-centromere (ACA) and anti RNA polymerase I/III (ARA). Other disease-specific auto antibodies which occur less commonly include anti-Th/To, anti U3- RNP and anti-PM/Scl autoantibodies, associated with polymyositis/scleroderma overlap[18]. None SSc-specific autoantibodies include anti-Ro (SS-A) and anti-La (SS-B), most often found in systemic lupus erythematosous and Sjogren's syndrome, anti-RNA polymerase II, also found in SLE and overlap syndromes, anti-Sm antibodies usually found in SLE, and anti U1-RNP associated with what was previously termed "mixed connective tissue disease". Whether these autoantibodies play a direct pathogenetic role or are simply epiphenomena is unknown. However, they have clear clinical utility as markers of different subsets of disease with characteristic patterns of organ involvement, and, as mentioned later, may well identify genetic subsets of the disease. The two main types of lung involvement, ILD or isolated pulmonary hypertension, are very tightly associated with specific auto-antibodies.

Antitopoisomerase Antibodies (ATA), present in approximately 20% of patients, are strongly linked to the development of lung fibrosis. Roughly half of SSc

patients in whom pulmonary fibrosis develops have ATA antibodies; conversely, most patients (>85%) with ATA positivity have pulmonary fibrosis. Some studies, but not all, suggest that ATA is also predictive of higher rates of progression of lung fibrosis[19]. The less frequent anti-nucleolar antibodies, anti-U3 RNP antibody and anti TH/To, are also associated with an increased risk of pulmonary disease; the latter also seem to be associated with development of pulmonary hypertension disproportionate to the degree of interstitial involvement[20]. Interestingly, anti TH/To have also been described in a subgroup of patients with clinical idiopathic pulmonary fibrosis and a UIP pattern on histology; the prognosis of these patients did not differ from those with IPF but no autoantibodies, lending support to the suggestion that Th/To autoantibodies may be markers of aggressive lung disease[21]. Microvascular injury is believed to be the earliest and possibly the primary event in the pathogenesis of SSc[22]. Outside of the lungs, Raynaud's phenomenon precedes the onset of skin fibrosis often by several years in most patients. In the lungs, a study of post-mortem lung tissue identified excessive formation of irregularly shaped alveolar capillaries with an increase in the number of endothelial cells in the early stages of lung fibrosis[23]. Although vascular abnormalities almost certainly precede fibrosis, the sequence of events and interplay with autoimmunity is not at all clear. It has been suggested that microvascular injury induces inflammation and autoimmunity, which in turn have direct and indirect roles in inducing fibroblast activation, a key event in the development of fibrosis [24]. Fibroblasts are the main cell type responsible for the excessive extracellular matrix synthesis and deposition seen in fibrosing lung disorders. Fibroblasts can differentiate into a more metabolically active cell with features intermediate between fibroblasts and smooth muscle cells, termed myofibroblast. Myofibroblasts express high levels of □-smooth muscle actin and synthesize increased levels of collagens, TIMP and other ECM components *in vitro*[25]. Fibroblasts explanted from SSc-ILD lungs have been shown to be phenotypically different from control lung fibroblasts, although there is a degree of heterogeneity in this cell population. SSc fibroblasts are considered to be in an activated state and the proportion of alpha-smooth muscle actin positive cells is elevated in cultures of SSc fibroblasts[26]. An intriguing question regards the origin of the stimulated fibroblasts; traditionally, they were believed to derive from the activation of resident fibroblasts induced by *in situ* cytokines and growth factors. However, accumulating evidence suggests that in fibrotic lung disease, interstitial lung fibroblasts can derive from at least two additional sources, the trans-differentiation of epithelial cells into myofibroblasts[27], and from a circulating fibroblast-like cell, the fibrocyte, derived from bone marrow stem cells, in response to cytokines and chemokines produced at the site of lung injury/ inflammation[29]. It is possible that all three mechanisms are operating in SSc-ILD, although the relative contribution of each cell type has yet to be delineated. It is unclear what environmental or genetic factors may contribute to the development of ILD in SSc. While environmental triggers have been postulated in the pathophysiology of SSc in general and environmental exposures such as polyvinylchloride and an impurity in one preparation of L-tryptophan have been known to trigger scleroderma like syndromes, there has never been a clearly established environmental link. Moreover, there has never been an environmental exposure implicated specific to ILD associated with SSc. Evidence suggests that gastroesophogeal reflux may contribute to the onset or progression of the disease, although the exact role of this reflux remains poorly understood[48]. A genetic contribution to scleroderma is supported by observed familial aggregation, ethnic predispositions, gene association studies and genome wide studies[30]. Pedigrees have been described that demonstrate members with SSC as well as members with ILDs not known to be related to SSc in numbers higher than would be expected by chance, suggesting a shared genetic predisposition between SSc, SSc ILD and non SSc ILD. The heterogeneous nature of SSc complicates the interpretation of genetic studies and is a significant barrier to defining the genetic basis of SSc. Better characterization of phenotype may aid the understanding of scleroderma in general and the development of ILD specifically[30]. Genome wide profiling is a recent advance that has begun to tease out specific signatures that correlate with different manifestations of SSc. For example, activation of genes controlled by TGF-beta is seen more often in patients with interstitial lung disease[31]. This type of understanding will enhance studies of genetic factors related to SSc and will promote targeted therapeutic developments for different subtypes of scleroderma including those with ILD.

Diagnosis of lung disease in scleroderma

Respiratory symptoms in scleroderma lung disease can be quite nonspecific. At early stage, for instance, pulmonary fibrosis can advance without any symptoms. Dyspnea on exertion is the symptom usually first noticed which progresses until it presents at rest. The cough is often dry and non-productive. The tightness of chest is often reported, along with some nonspecific symptoms for instance the fatigue. Dyspnea could be due to ILD, some infrequent pulmonary manifestations, such as bronchiectasis, diffuse alveolar hemorrhage or its cause could be extra pulmonary like cardiac involvement, especially the left ventricular diastolic dysfunction, diminished thoracic cage expansions, neuromuscular, and pleural disease. It is rather challenging for the clinician to detect the underlying causes not only of breathlessness, but also other symptoms which can be due to different or even multiple causes, like fatigue. Fatigue may be seen in scleroderma lung disease, but also in active arthritis, myositis, fibromyalgia, or cardiac disease. Physical examination of the scleroderma patients is of utmost importance. It is to note that there is a minor group of patients with ILD, in which the ILD is

the first, initial sign of scleroderma[32]. The examination is usually rewarding as in most cases there are some signs that point to scleroderma if the search is thorough. The involvement of the lungs in scleroderma may be detected by auscultation, as in some patients the bibasilar late inspiratory fine crackles are identified. Examination findings of the pre-cordium may have a loud pulmonary component of second heart sound which is fixed or paradoxical split. If cor pulmonale develops, the signs are high-pitched systolic murmur of tricuspid regurgitation, hepatomegaly, a pulsatile liver, ascites, and peripheral edema.

Pulmonary function testing

Pulmonary Function Testing (PFTs) is an important component of the evaluation of dyspnea and in the detection of pulmonary involvement in patients with SSc. Patients with significant interstitial lung disease will demonstrate restriction on lung function testing although normal pulmonary function may be present in mild disease. Total Lung Capacity (TLC) by means of plethysmography is the most reliable measure of restriction and will confirm the presence of true lung restriction. However, spirometry which is more typically utilized in clinical practice provides a good estimation of true restriction. Spirometry provides measures of the Forced Vital Capacity (FVC) and the forced expiratory volume in one second (FEV1). In a restrictive lung disease, the FVC should be reduced and the FEV1/FVC ratio should be normal. It has been estimated that 40% patients with scleroderma have a FVC of less than 75% predicted, marking the presence of ILD[33]. The diffusing capacity (DLCO) provides a measure of gas transfer between the air inhaled into the alveoli to the red blood cells in the systemic circulation. The DLCO is one of the most valuable measures in the evaluation of the scleroderma patients as a decreased value may be the earliest signal of lung disease in SSc and is reduced in 70% of SSc patients[34]. Moreover, the DLCO correlates most closely with the degree of disease seen on the High Resolution Computed Tomography (HRCT) scan. The DLCO will be reduced in both pulmonary hypertension and ILD. Thus, the DLCO is not specific for the diagnosis of SSc ILD.

Radiology

The characteristic chest X-ray in scleroderma patients with ILD shows linear and reticular pattern, superimposed upon the ground-glass attenuation. Traction bronchiectasis may be detected, but contrary to the finding in Idiopathic Pulmonary Fibrosis (IPF), the honeycombing is rare. Evidence of pulmonary disease has been described in chest X-rays in 20–65% of patients affected by scleroderma[35]. As with histology, the high resolution CT pattern in SSc-ILD is relatively homogeneous, again differing from other CTD-associated interstitial lung diseases, where a greater variety is present. In SSc-ILD, the most frequent CT pattern is either predominant ground-glass opacification or an admixed ground glass/reticulation pattern, with a predominant reticular pattern present in only one third of patients. In contrast, SSc-ILD and idiopathic Non-Specific Interstitial Pneumonia (NSIP) are less extensive, less coarse, and characterised by a greater proportion of ground glass opacification than IPF, supporting the biopsy series stating that NSIP is by far the commonest histological pattern in SSc-ILD[35]. Ground glass on CT can represent either predominant inflammatory changes or fibrosis subliminal to the limits of resolution of HRCT. Although it is impossible to distinguish fibrosis from inflammation with certainty on the basis of HRCT, features suggestive of established fibrosis include admixed reticular abnormalities and the presence of traction bronchiectasis[36]. However, even in the presence of these features, at least some of the ground glass may represent inflammatory changes, and the HRCT pattern can only be used as a rough guide in predicting possible reversibility with treatment.

Bronchoalveolar Lavage (BAL)

The role of BAL in patients with SSc ILD is controversial and in evolution. When a cell count is done on BAL from patients with SSc associated ILD, elevated numbers of granulocytes may be seen, especially neutrophils and eosinophils. Increased numbers of lymphocytes and mast cells may also be seen. Early studies correlated increased granulocytes in BAL with increased response to immunosuppression presumably because this represented active alveolitis[38]. Subsequently, BAL granulocytosis has been shown to correlate with the degree of ground glass opacity seen on HRCT and with more advanced interstitial disease[37]. However, data from the Scleroderma Lung Study suggest that BAL granulocytosis does not add any additional prognostic information to HRCT and pulmonary function measures and is not a predictor of treatment response[38].

Biopsy

Similar to radiographic appearances, there are a variety of histologic subtypes found in SSc ILD. In one series, NSIP was the more common histopathology occurring in 76% of the cases[39]. In this same series, UIP occurred in 11% of the cases. There were also rare cases of organizing pneumonia and diffuse alveolar damage. Importantly, the clinical outcome does not correlate with the observed histology[39]. Patients with scleroderma ILD can often experience stabilization after the initial development of their lung disease. In a series of 80 patients, survival does not differ between cellular NSIP, fibrotic NSIP and UIP. Thus, histology has no prognostic value. These patterns are in stark contrast to idiopathic ILDs where UIP is the most common pathology, the pathologic finding of UIP is associated with a poorer prognosis and stabilization of UIP for decades is rarely seen. Given this data, there is little value to a surgical biopsy in the evaluation of a

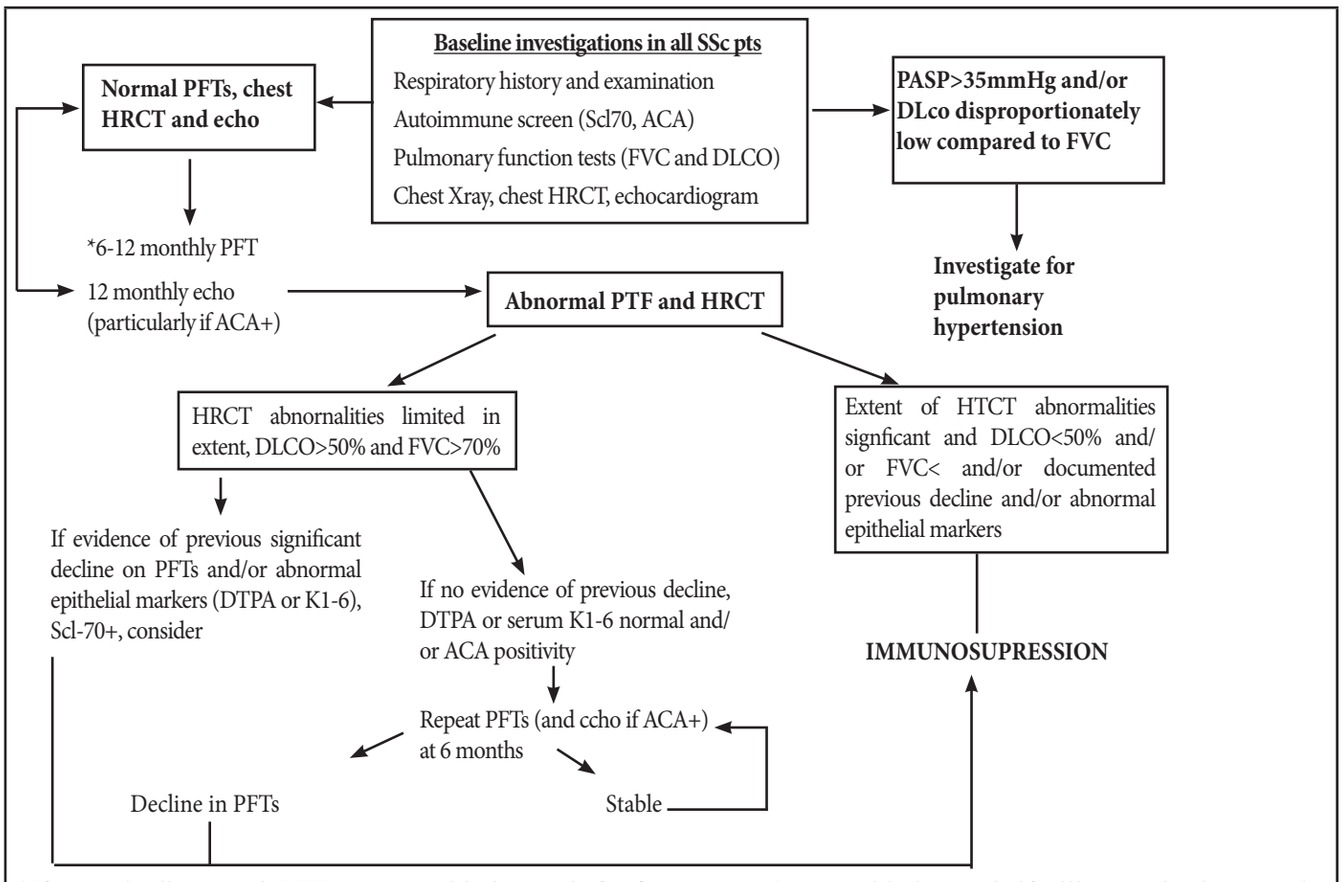
patient with scleroderma associated ILD. The exception to this may be in cases of an unusual CT pattern which does not fit a predicted pattern seen in SSc.

Isotope lung scans: To identify active lung inflammation in ILD or pulmonary emboli in PAH. Doppler echocardiography supplemented by electrocardiogram (ECG), are the traditional methods for investigating possible PAH, but their results can be misleading in scleroderma patients and definitive diagnosis requires direct measurement of Pulmonary Artery Pressure (PAP) by right heart catheterization. In ILD the echocardiogram is checked for pulmonary regurgitation and the pulmonary arterial systolic pressure is measured. If there is pulmonary regurgitation, the peak measurement is checked, and the size of the right ventricle is also checked to determine the amount of additional strain.

Right heart catheterisation: By passing a catheter through a vein into the heart, pressures in the heart chambers and major blood vessels leading from the heart to the lungs can be measured directly. Right heart catheterization remains the gold standard for diagnosis of PH. Apart the fact that PH is precisely estimated, the acute vasodilatation testing is also performed with inhaled nitric oxide, IV epoprostenol, or IV adenosine in order to determine the reversibility upon application of vasodilators, thus choosing the most appropriate treatment for a given patient. In patients with scleroderma, it is very important to rule out the existence of the left-sided heart disease, which is a frequent cause of PH in these patients. The right heart catheterization is the only method by which it can be ruled out.

Monitoring and initiating treatment

Recommended investigations at baseline include PFT, chest X-ray, HRCT chest and echocardiogram. Serial monitoring of lung function tests, particularly in the first 5 years after diagnosis, is crucial for detection of onset and/or progression of SSc-ILD. HRCT chest can be omitted at baseline in ACA positive patients with normal PFTs, in view of the extremely low frequency of significant interstitial lung disease in this group. Immunosuppression should be considered in patients with severe and/or progressive disease. A cut-off of DLCO< 50% and/or FVC<70% together with significant extent of abnormalities on HRCT can be used to define severe disease and initiate treatment, unless there is documented stability on sequential PFTs over several years. Although not available in all centers, epithelial permeability markers such as DTPA clearance or serum Kl-6, are powerful predictors of subsequent progression in SSc-ILD, and should be used in conjunction with other parameters.



Algorithm for monitoring and initiating treatment for interstitial lung disease in patients with systemic sclerosis[40]

Therapies

Therapy for interstitial lung disease will not reverse scarring that has already taken place so it is important to diagnose and treat the condition as early as possible. The goals of treatment are to improve walking distance, dyspnea and quality of life. Unfortunately the rationalization of treatment has been hampered by a lack of enough double-blinded studies. The decision on who and when to treat is made by considering whether there is evidence of recent progression of the disease. Deterioration can be assessed by serial pulmonary function tests or chest radiography, duration and by autoantibody status. If there is a significant risk of disease progression and the risks associated with treatment (likely side-effects) are clearly outweighed by the risks associated with failure to treat (likely progression of disease) treatment should be introduced but it should be delayed if it is clear that disease is trivial and likely to remain stable. This judgment is sometimes very straightforward, but often the decision is a very close call and may require extra tests. Ideally, the patient should be introduced to these concepts and should then participate fully in decisions. Corticosteroids such as prednisolone or methylprednisolone may be given to reduce the inflammation. Due to concerns of an increased risk of scleroderma renal crisis high doses of corticosteroids are seldom used, although low doses (e.g. prednisone 10mg daily) continue to be prescribed, often in combination with immunosuppressive therapy. For some patients, steroids will help decrease inflammation and cause a dramatic improvement in symptoms while other patients may experience only partial improvement. Response to treatment depends on the amount of inflammation present and improvement may not be seen for up to 6-12 weeks.

A chest X-ray, exercise tests and pulmonary function tests will determine whether a patient's condition has been stabilized or improved. Cyclophosphamide may be used alone or in combination with steroids to reduce inflammation by killing some inflammatory cells and suppressing their function. These medications may take six months or longer to show improvement. Side effects include gastrointestinal irritation, bladder inflammation, bone marrow suppression, infection, irregular menstruation and blood disorders. The Scleroderma Lung Study evaluated 162 patients randomized to receive either placebo or oral cyclophosphamide (in addition to low dose prednisolone) for one year[41]. The study met the primary outcome, the observed absolute difference in FVC% at 12 months between treated and untreated patients, although the difference was small. Interestingly, the largest effect was seen in patients with more severe lung fibrosis, as assessed by CT scoring, emphasizing the importance of patient selection[41]. Among secondary outcome measures, a significant, but again small, beneficial effect was observed in the skin thickness and dyspnea scores. Oral versus intravenous cyclophosphamide as evidenced by oral cyclophosphamide Scleroderma Lung Study have the same magnitude in terms of outcome. The difference is IV cyclophosphamide is less toxic (hematuria, haemocytopenia) than oral cyclophosphamide. Furthermore, although long term follow up data was lacking, experience gained in the treatment of other autoimmune disorders, indicates that intermittent monthly iv boluses of cyclophosphamide are associated with lower risks of cancer and gonadal failure compared to oral daily administration of the drug[42]. Unresolved issues regarding treatment include which long-term immunosuppressive agents to use after the induction period with cyclophosphamide, so as to minimize cyclophosphamide-induced morbidities.

The immunosuppressant azathioprine can be used as maintenance following induction with cyclophosphamide as shown in the FAST trial. The FAST trial (fibrosing alveolitis in scleroderma trial) performed in 45 patients, comparing placebo with monthly intravenous cyclophosphamide for 6 months, followed by oral azathioprine and low dose prednisone for a total of 24 months[43]. Although this study did not reach a significant result, there was a clear trend towards a difference in change in FVC at one year in the treatment group ($p=0.08$), with a 4.19% change in FVC at one year favouring the treatment group. The similar results obtained in the FAST trial in which six months of cyclophosphamide were followed by azathioprine, suggest that a protocol of induction (with cyclo) / maintenance (with less toxic immunosuppressants) regimen is a viable option. Though it has been proven inferior in efficacy to corticosteroids and/or cyclophosphamide, azathioprine can be given to patients who have problems tolerating the side effects of corticosteroids and/or cyclophosphamide as first line treatment protocol. Side effects of azathioprine may include fever, skin rash, gastrointestinal irritation and blood disorders. Other immunosuppressants, such as cyclosporine and tacrolimus may also be used. However, cyclosporine can cause renal impairment while tacrolimus can cause type 2 diabetes. Both colchicine and D-penicillamine are occasionally prescribed. Both agents have the advantage that major toxicity is rare. However, there is a complete lack of compelling circumstantial evidence that either treatment is effective in lung disease. Their use can therefore be seriously questioned, especially if it results in delays in starting more effective treatment.

A group of medications currently being developed are the antifibrotic agents which act directly to limit scar tissue formation. These agents are not available routinely but are being investigated around the world in clinical trials. The endothelin receptor antagonist bosentan (Tracleer) has already been shown to be effective in patients with scleroderma and PAH. It is being studied in patients with ILD associated with scleroderma as well as patients with idiopathic pulmonary fibrosis. Endothelin (ET-1) is a key mediator of disease processes in PAH levels of ET-1 are elevated in PAH and can cause vasoconstriction, inflammation, fibrosis and vascular hypertrophy. This is through binding to two receptor subtypes, ETA and ETB. Novel therapies include ETA antagonist sitaxsentan,

which is currently being investigated in PAH and has shown positive results as it significantly improved exercise capacity and cardiopulmonary haemodynamics during a 12-week trial in a group of PAH patients including those with connective tissue disease. Final data are still to be established on the use of this compound in PAH[45]. Ambrisentan, another ETA antagonist, is being evaluated and preliminary results show improvements in exercise capacity and haemodynamics. There are randomized clinical trials currently ongoing on ambrisentan to further explore its efficacy and side effects[46]. Novel immunomodulatory treatments (such as the tumour necrosis factor inhibitors infliximab (Remicade) and etanercept (Enbrel)) are being studied in patients with idiopathic pulmonary fibrosis. The disease modifying anti-rheumatic drug methotrexate may also be used. Studies are also ongoing with an anti-CTGF (connective tissue growth factor) antibody and with subcutaneous recombinant interferon-g1b in patients with idiopathic pulmonary fibrosis. Oxygen therapy may be prescribed for some people with IPF to increase the amount of oxygen in the blood. The need for oxygen depends on the severity of disease and activity level. Supplemental oxygen may help reduce shortness of breath and prevent other complications and may allow those affected by ILD to feel better and lead a more active life.

Rituximab is a chimeric monoclonal antibody against human CD20 that depletes peripheral B cells. It has been introduced with some success in the treatment of systemic rheumatic diseases and exhibits an acceptable safety profile. In the pathogenesis of scleroderma evidence suggests B cells may be actively involved in the fibrotic process[12]. B cells are over activated in both experimental models of fibrosis as well as in humans with SSc . Rituximab has been tried in SSc with promising results[12]. In a randomized controlled study it was shown that treatment with two courses of rituximab leads to a significant improvement of lung function at one year compared to baseline[46]. The study was not able to exactly say how rituximab mediates its beneficial effects in SSc. However, rituximab seems to have a broad effect on the immune system, beyond B cell depletion, and therefore other mechanisms may apply eg significant decrease in Platelet Derived Growth Factor (PDGF) receptor expression and activation in the skin[47]. They also noted it had a better safety profile. Recently, the Rituximab group of EUSTAR reported encouraging results in 72 patients with SSc treated with rituximab[52]. We still need more randomized studies with larger numbers of participants. If rituximab turns out to be effective, it would be a major therapeutic advance in SSc since it can be administered on a long term basis due to its acceptable safety profile.

Lung transplantation may offer hope for some people with severe ILD. Until recently, very little data was available on the outcome of lung transplantation in scleroderma, with only a handful of cases found in the published literature[48]. Schachna *et al*[48] in a study compared long term survival in 29 patients with scleroderma, 70 with IPF and 38 with idiopathic pulmonary hypertension, representing the total number of transplants for these conditions in two US centers over a 12 and half year period following lung transplants. Indications for transplantation amongst those with scleroderma were interstitial lung disease in 15 patients, pulmonary arterial hypertension in 11 and both in three patients. Despite the common perception that systemic disorders may be a contraindication to transplant, the study concluded that scleroderma patients undergoing lung transplantation have similar rates of survival to the two other lung-only disorders at two years, although there was a non-significant trend towards a higher early mortality within the first six months. There is need for more research on transplantation in scleroderma.

Future directions

In view of the toxicities of the current immunosuppressive regimens and poor outcomes of patients despite being on optimal current management, alternative, more effective treatment options are needed. The activation of T and B cells early in the course of the disease suggests that these cells and their cytokines are potential targets for therapeutic interventions[49]. Approaches that alter the balance between TH1 and TH2 cytokines by inhibiting TH2 cytokines, have been shown to be beneficial in animal models of SSc[50]. Another potential source of hope would be pro-fibrotic cytokines, TGFβ and CTGF. These are natural treatment targets, and have been evaluated in a Phase I/II trials to assess safety and tolerability though the results have been largely disappointing[51]. Despite the recent advances in therapies still the prognosis of pulmonary manifestations of scleroderma is poor. Further understanding of the molecular mechanisms through which vascular disease, autoimmunity and fibrosis interlink will inevitably lead to improved treatment strategies in SSc.

Conclusions

Pulmonary complications are common in SSc and are the leading causes of death. Careful evaluation by the clinician is warranted to detect the presence of an ILD and to select patients appropriately for consideration of therapy. Exertional dyspnea and dry cough are the most common presenting symptoms in patients with SSc who develop pulmonary involvement. Early initiation of therapy should be particularly considered in patients with early disease, clinical progression and evidence of alveolitis. Unfortunately, systemic sclerosis lung disease is often not detected or diagnosed until the late stages, particularly in those who did not develop the classic signs of skin-hardening or sclerodactyly, or those who only exhibited subtle respiratory symptoms. At the current time, cyclophosphamide remains the best studied therapeutic agent although alternatives are actively being evaluated. The pathogenesis of SSc-ILD is still an enigma and is being actively researched. This will advance our understanding of the disease and ability to care for these patients. Clinical trials are underway and

offer hope for novel approaches to this mysterious and often devastating manifestation of scleroderma.

References

1. Steen VD, Medsger TA Jr. Severe organ involvement in systemic sclerosis with diffuse scleroderma. *Arthritis Rheum*. 2000; **43**(11):2437–2444. [PubMed: 11083266].
2. Ferri C, Valentini G, Cozzi F, Sebastiani M, Michelassi C, *et al*. Systemic sclerosis: demographic, clinical, and serologic features and survival in 1,012 Italian patients. *Medicine* (Baltimore). 2002; **81**: 139-153.
3. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972-2002. *Ann Rheum Dis*. 2007; **66**:940-944.
4. Mathai SC, Hummers LK, Champion HC, *et al*. Survival in pulmonary hypertension associated with the scleroderma spectrum of diseases: impact of interstitial lung disease. *Arthritis Rheum.* 2009; **60**(2):569–577. [PubMed: 19180517].
5. Steen V, Medsger TA, Jr. Predictors of isolated pulmonary hypertension in patients with systemic sclerosis and limited cutaneous involvement. *Arthritis Rheum*. 2003; **48**: 516-522.
6. Ungerer RG, Tashkin DP, Furst D, *et al.* Prevalence and clinical correlates of pulmonary arterial hypertension in progressive systemic sclerosis. *Am J Med.* 1983; **75**: 65-74.
7. Thompson AE, Pope JE. A study of the frequency of pericardial and pleural effusions in scleroderma. *Br J Rheumatol.* 1998; **37**: 1320-1323.
8. Lang B, Ortlieb H, Meske S, Hauke G, Peter HH. Progressive systemic sclerosis presenting with spontaneous pneumothorax. *J Rheumatol.* 1989; **16**: 254- 256.
9. Hill CL, Nguyen AM, Roder D, Roberts-Thomson P. Risk of cancer in patients with scleroderma: a population based cohort study. *Ann Rheum Dis.* 2003; **62**: 728-731.
10. Yang Y, Fujita J, Tokuda M, Bandoh S, Ishida T. Lung cancer associated with several connective tissue diseases: with a review of literature. *Rheumatol Int.* 2001; **21**: 106-111.
11. Nihtyanova SI, Tang EC, Coghlan JG, *et al*. Improved survival in systemic sclerosis is associated with better ascertainment of internal organ disease: a retrospective cohort study. *Q J Med*. 2010; **103**:109-115.
12. Atamas SP, Yurovsky VV, Wise R, Wigley FM, Goter Robinson CJ, *et al*. Production of type 2 cytokines by CD8+ lung cells is associated with greater decline in pulmonary function in patients with systemic sclerosis. *Arthritis Rheum.* 1999; **42**: 1168-1178.
13. Bogatkevich GS, Ludwicka-Bradley A, Singleton CB, Bethard JR, Silver RM. Proteomic analysis of CTGF-activated lung fibroblasts: identification of IQGAP1 as a key player in lung fibroblast migration. *Am J Physiol Lung Cell Mol Physiol.* 2008; **295**: L603-L611.
14. Selman M, King TE, Pardo A. Idiopathic pulmonary fibrosis: prevailing and evolving hypotheses about its pathogenesis and implications for therapy. *Ann Intern Med.* 2001; **134:** 136-151.
15. Fujii H, Hasegawa M, Takehara K, Mukaida N, Sato S. Abnormal expression of intracellular cytokines and chemokine receptors in peripheral blood T lymphocytes from patients with systemic sclerosis. *Clin Exp Immunol.* 2002; **130**: 548-556.
16. Prescott RJ, Freemont AJ, Jones CJ, Hoyland J, Fielding P. Sequential dermal microvascular and perivascular changes in the development of scleroderma. *J Pathol.* 1992; **166**: 255-263.
17. Rottoli P, Magi B, Perari MG, *et al.* Cytokine profile and proteome analysis in bronchoalveolar lavage of patients with sarcoidosis, pulmonary fibrosis associated with systemic sclerosis and idiopathic pulmonary fibrosis. *Proteomics*. 2005; **5**: 1423-1430.
18. Oddis CV, Okano Y, Rudert WA, Trucco M, Duquesnoy RJ, Medsger TA Jr. Serum autoantibody to the nucleolar antigen PM-Scl. Clinical and immunogenetic associations. *Arthritis Rheum*. 1992; **35**: 1211-1217.
19. Briggs DC, Vaughan RW, Welsh KI, Myers A, duBois RM, Black CM. Immunogenetic prediction of pulmonary fibrosis in systemic sclerosis. *Lancet.* 1991; **338**: 661-662.
20. Steen VD, Powell DL, Medsger TA, Jr. Clinical correlations and prognosis based on serum autoantibodies in patients with systemic sclerosis. *Arthritis Rheum*. 1988; **31**: 196-203.
21. Fischer A, Pfalzgraf FJ, Feghali-Bostwick CA, *et al*. Anti- th/to-positivity in a cohort of patients with idiopathic pulmonary fibrosis. *J Rheumatol*. 2006; **33**: 1600-1605.
22. Kahaleh MB, Sherer GK, LeRoy EC. Endothelial injury in scleroderma. *J Exp Med.* 1979; **149:** 1326-1335.
23. Beon M, Harley RA, Wessels A, Silver RM, Ludwicka- Bradley A. Myofibroblast induction and microvascular alteration in scleroderma lung fibrosis. *Clin Exp Rheumatol*. 2004; **22**: 733-742.
24. Abraham DJ, Varga J. Scleroderma: from cell and molecular mechanisms to disease models. *Trends Immunol.* 2005; **26**: 587-595.
25. Kirk TZ, Mark ME, Chua CC, Chua BH, Mayes MD. Myofibroblasts from scleroderma skin synthesize elevated levels of collagen and tissue inhibitor of metalloproteinase (TIMP-1) with two forms of TIMP-1. *J Biol Chem.* 1995; **270**: 3423-3428.
26. Jelaska A, Korn JH. Role of apoptosis and transforming growth factor beta1 in fibroblast selection and activation in systemic sclerosis. *Arthritis Rheum.* 2000; **43**: 2230-2239.
27. Kim DS, Yoo B, Lee JS, *et al*. The major histopathologic pattern of pulmonary fibrosis in scleroderma is nonspecific interstitial pneumonia. *Sarcoidosis Vasc Diffuse Lung Dis*. 2002; **19**: 121-127.

28. Lama VN, Phan SH. The extrapulmonary origin of fibroblasts: stem/progenitor cells and beyond. *Proc Am Thorac Soc.* 2006; **3**: 373-376.
29. Carlo-Stella N, Belloli L, Barbera R, Gambaro C, Rando G, *et al*. Gastroesophageal reflux and lung disease in systemic sclerosis. *Am J Respir Crit Care Med.* 2009; **179**: 1167.
30. Agarwal SK, Tan FK, Arnett FC. Genetics and genomic studies in scleroderma (systemic sclerosis). *Rheum Dis Clin North Am.* 2008; **34**: 17-40.
31. Sargent JL, Whitfield ML. Capturing the heterogeneity in systemic sclerosis with genome-wide expression profiling. *Expert Rev Clin Immunol.* 2011; **7**: 463-473.
32. Van der Kamp R, Tak PP, *et al*. Interstitial lung disease as the first manifestation of systemic sclerosis. *Neth J Med.* 2007; **65**:390-394.
33. Highland KB, Silver RM. New developments in scleroderma interstitial lung disease. *Curr Opin Rheumatol.* 2005; **17**: 737-745.
34. Wells AU, Hansell DM, Rubens MB, King AD, Cramer D, *et al*. Fibrosing alveolitis in systemic sclerosis: indices of lung function in relation to extent of disease on computed tomography. *Arthritis Rheum.* 1997; **40**: 1229-1236.
35. Desai SR, Veeraraghavan S, Hansell DM, *et al*. CT features of lung disease in patients with systemic sclerosis: comparison with idiopathic pulmonary fibrosis and nonspecific interstitial pneumonia. *Radiology.* 2004; **232**: 560-567.
36. Desai SR, Wells AU, Rubens MB, du Bois RM, Hansell DM. Traction bronchiectasis in cryptogenic fibrosing alveolitis: associated computed tomographic features and physiological significance. *Eur Radiol.* 2003; **13**: 1801- 1808.
37. Goldin JG, Lynch DA, Strollo DC, Suh RD, Schraufnagel DE, *et al.* High resolution CT scan findings in patients with symptomatic scleroderma-related interstitial lung disease. *Chest.* 2008; **134**: 358-367.
38. Strange C, Bolster MB, Roth MD, Silver RM, Theodore A, *et al*. Bronchoalveolar lavage and response to cyclophosphamide in scleroderma interstitial lung disease. *Am J Respir Crit Care Med.* 2008; **177**: 91-98.
39. Bouros D, Wells AU, Nicholson AG, Colby TV, Polychronopoulos V, *et al*. Histopathologic subsets of fibrosing alveolitis in patients with systemic sclerosis and their relationship to outcome. *Am J Respir Crit Care Med.* 2002; **165**: 1581-1586.
40. Renzoni EA. Interstitial lung disease in systemic sclerosis. Review. *Monaldi Arch Chest Dis*. 2007; **67**:217-28.
41. Tashkin DP, Elashoff R, Clements PJ, *et al*. Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med.* 2006; **354:** 2655-2666.
42. Petri M. Cyclophosphamide: new approaches for systemic lupus erythematosus. *Lupus*. 2004; **13**: 366-371.
43. Hoyles RK, Ellis RW, Wellsbury J, *et al.* A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. *Arthritis Rheum.* 2006; **54**: 3962-3970.
44. Barst RJ, Langleben D, Frost A, *et al* and the STRIDE-1 Study Group. Sitaxsentan therapy for pulmonary arterial hypertension. *Am J Respir Crit Care Med.* 2004;**169**: 441-447.
45. Galie N, Bade sch BD, Oudiz R, Simonneau G, McGoon, *et al*. Ambrisentan therapy for pulmonary arterial hypertension. *J Am Coll Cardiol.* 2005; **46:** 529-535.
46. Daoussis D, Liossis SN, Tsamandas AC, Kalogero-poulou C, Kazantzi A, *et al*. Experience with ritux-imab in scleroderma: results from a 1-year, proof-of-principle study. *Rheumatology* (Oxford) 2010; **49**: 271-280.
47. Daoussis D, Tsamandas AC, Liossis SN, Antonopoulos I, Karatza E, *et al*. B-cell depletion therapy in patients with diffuse systemic sclerosis associates with a significant decrease in PDGFR expression and activation in spindle-like cells in the skin. *Arthritis Res Ther.* 2012; **14**: R145.
48. Schachna L, Medsger TA, Dauber JH, *et al*. Lung transplantation in scleroderma compared with idiopathic pulmonary fibrosis and idiopathic pulmonary arterial hypertension. *Arthritis Rheum.* 2006; **54**: 3954-3961.
49. Chizzolini C, Parel Y, Scheja A, Dayer JM. Polarized subsets of human T-helper cells induce distinct patterns of chemokine production by normal and systemic sclerosis dermal fibroblasts. *Arthritis Res Ther.* 2006; **8**: R10.
50. Ushiyama C, Hirano T, Miyajima H, Okumura K, Ovary Z, Hashimoto H. Anti-IL-4 antibody prevents graft-versus- host disease in mice after bone marrow transplantation. The IgE allotype is an important marker of graftversus- host disease. *J Immunol.* 1995; **154**: 2687-2696.
51. Denton CP, Merkel PA, Furst DE, *et al.* Recombinant human anti-transforming growth factor beta1 antibody therapy in systemic sclerosis: a multicenter, randomized, placebo-controlled phase I/II trial of CAT-192. *Arthritis Rheum.* 2007; **56**: 323-333.