Interstitial lung disease in systemic sclerosis

L. Mouthon¹, A. Berezné¹, M. Brauner², M. Kambouchner³, L. Guillevin¹, D. Valeyre⁴

Summary

Introduction  Interstitial lung disease (ILD) associated with systemic sclerosis (SSc) is mainly encountered in patients with diffuse disease although it may occur less frequently in patients with limited cutaneous disease.

Background  ILD should be detected early in the course of the disease with the help of high resolution computerised tomography (HRCT) and pulmonary function tests (PFT). Altogether, up to 75% of SSc patients develop ILD. However, ILD is progressive in only a minority of patients. Unlike idiopathic ILD, SSc associated ILD corresponds to non-specific interstitial pneumonia (NSIP) in most cases, whereas usual interstitial pneumonia (UIP) is encountered less frequently. This explains the better prognosis of SSc associated ILD compared to idiopathic ILD. Nevertheless, ILD represents one of the two main causes of death in SSc.

Viewpoint  The treatment of SSc associated ILD is not very well established. Anti-fibrosing treatments have failed to demonstrate any benefit and cyclophosphamide, which has been used in the treatment of this condition for about 15 years, has recently been evaluated in two prospective randomised studies which showed a significant but modest effect on respiratory function.

Conclusion  A subgroup of patients with rapidly progressive ILD might benefit from pulsed intravenous cyclophosphamide combined with prednisone 15 mg daily but this remains to be confirmed.

Key-words: Diffuse pulmonary infiltration • Systemic sclerosis • Non-specific interstitial pneumonia • Cyclophosphamide.
Introduction

Systemic sclerosis (SSc) is a generalised disorder of connective tissue, arterioles and the microvasculature, characterised by the accumulation of extracellular matrix, an obliterative vasculitis and the presence of cellular and humoral immune perturbations [1]. Depending on the degree and extent of the cutaneous involvement three forms can be distinguished: the diffuse cutaneous forms of the disease characterised by sclerotic lesions extending above the elbows and the knees and possibly involving the trunk [2]; the limited cutaneous forms, in the course of which sclerotic lesions involve the extremities but do not extend above the elbows and knees; and the limited forms in which the skin is spared [3].

SSc has a predilection for females aged between 45 and 64 years. Its prevalence is still poorly understood, estimated in the United States and Australia at between 200 and 260 cases per million of population, in Asia between 20 and 50 per million and in Europe between 100 and 200 per million [1]. We have found a prevalence of 158 per million in the department of Seine Saint-Denis [4], which, by extrapolation, gives an estimate of between 6000 and 9000 patients suffering from SSc in France.

Pulmonary involvement is common in the course of SSc and, taken together, interstitial lung disease (ILD) and pulmonary hypertension are considered, at present, to be the two main causes of death in this disease [5].

The finding of predominantly basal pulmonary fibrosis constitutes one of the three minor diagnostic criteria for the diagnosis of SSc, the other two being sclerodactyly (fig 1a) and evidence of scaring (fig 1b) or tissue loss of the finger tips; the presence of two of these three criteria supporting the diagnosis of SSc [6]. The major criterion supporting the diagnosis of SSc is the presence of sclerotic lesions extending above the metacarpo-phalangeal joints.

The other pulmonary lesions found during the course of SSc include aspiration pneumonia, pleural effusion, spontaneous pneumothorax, drug induced pneumonitis, associated pneumoconiosis and neoplasms [1].

Classification of interstitial lung diseases

With reference to the different entities belonging to the idiopathic interstitial lung diseases [7], those seen in the course of SSc may be classified on the basis of the histopathological data into: usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP), diffuse alveolar damage (DAD), organising pneumonia (OP) and lymphocytic interstitial pneumonia (LIP). Following several recent series based on surgical lung biopsies, the histological type most commonly found in the disease associated with SSC is NSIP (76%), followed by UIP (11%). In some cases the appearance is of fibrotic lung destruction and cannot be classified.

In SSc the most common types of diffuse infiltrating pneumonia are NSIP then UIP.

Pathophysiology

The pathophysiology of SSc is still poorly understood. The increased production of intra-cellular matrix proteins by fibroblasts results from abnormal interactions between endothelial cells, mononuclear cells (lymphocytes and monocytes) and fibroblasts, in a context of vascular hyperreactivity and tissue hypoxia [8]. We will not tackle here the total pathophysiology of SSc and we will concentrate on the mechanisms associated...
with the development of ILD in the course on SSc. The pulmonary fibrotic lesions are associated with an increased incidence of a class II MHC DR3/DR52a and/or the presence of anti-topoisomerase I (Scl-70) antibodies in the serum. The pathogenesis consists of a combination of inflammatory, destructive and fibrosing lesions. As in idiopathic pulmonary fibrosis both the pulmonary epithelial and endothelial lesions seem to be fundamental in the pathogenesis of SSc. During the reparative phase there is a secretion of type TH-2 cytokines, of which the most important is IL-4, which stimulate the proliferation of fibroblasts and the synthesis of collagen. T lymphocytes also appear to play an important role in the development of ILD in SSc. Histological study of lung biopsies shows evidence of lymphoid follicles and plasma cells. In addition, studies of gene expression have shown that the intra-alveolar CD8+ lymphocytes of patients presenting with a fibrosing pneumonitis synthesise IL-4 unlike those of patients with SSc without ILD [9].

An increased synthesis of IL-4 alone probably does not explain the increased production of matrix collagen. In fact, in a study comparing the levels of RNA coding for IL-4, IL-5 and interferon gamma (INF-γ) based on lung biopsies of patients with ideopathic pulmonary fibrosis (IPF) and pulmonary fibrosis associated with SSc, an increased synthesis of IL-4 and IL-5 was seen in the SSc patients but not in those with IPF [10]. In this study, the ratio IL-5/INF-γ was 22/1 in IPF and 2/1 in SSc while the levels of RNA coding for INF-γ were not significantly different between SSc patients and normal controls.

INF-γ is the most powerful inhibitor of the synthesis of extra-cellular matrix proteins by fibroblasts. INF-γ exerts an anti-fibroin effect in the course of pulmonary fibrosis induced by bleomycin in inhibiting the effect of TGF-γ on the augmentation of collagen synthesis [11, 12]. INF-γ synthesised by CD4+ lymphocytes inhibits, in a dose dependent way, the proliferation of fibroblasts in healthy subjects [11] as well as collagen synthesis. On the other hand, it has recently been reported that the inhibiting power of INF-γ on the synthesis of collagen by fibroblasts in SSc patients is greatly diminished. These results may explain the occurrence of collagenous fibrosis in patients with SSc.

Finally, one observes during the course of SSc, as in all fibrosing processes, the important role of oxidative stress, in particular an increase in the markers of lipid peroxidation [13], as well as an increase in other markers of oxidative damage such as protein oxidation products and nitrosothiols and a lowering of anti-oxidant defences estimated by measurement of total thiols [14]. In addition the monocytes of SSc patients produce in vitro larger quantities of superoxide anions than the monocytes of healthy subjects [15]. Skin fibroblasts from SSc patients spontaneously produce more free radicals than the fibroblasts of controls; this production depends on the activation of NADPH oxidase and the inhibition of this production by N-acetyl-cysteine leads to cellular deactivation and diminution of collagen production [16]. We have recently produced evidence that the serum of sclerodermics induces the production of different types of free radicals that selectively activate endothelial cells and fibroblasts leading to the development of vascular and fibrosing complications. The quantification of the production of free oxygen radicals induced by the serum may constitute a marker of activity of the disease and allows the selection of appropriate treatments.

**Clinical presentation**

The prevalence of diffuse ILD during the course of SSc is difficult to state accurately and may vary according to the study from 16 to 100% [6, 17-19]. Patients with SSc and ILD are asymptomatic for a long time and the discovery of early pulmonary involvement depends on the diagnostic methods used. Thus, in the series of Schurawitzki et al [20], 91% of the patients had evidence of ILD on high resolution CT scans while only 31% of the same patients showed abnormalities on the chest x-ray. When a chest x-ray is used for the detection of pulmonary involvement in SSc, the prevalence of ILD is up to 56%. It is 85-90% when CT is used.

ILD may develop in the course of limited cutaneous SSc but is much more common in the diffuse cutaneous forms. It then appears earlier (in the first three years), often in a more severe form at the onset. The progression of ILD, measured by the reduction in forced vital capacity (FVC), is more marked in the first years after the diagnosis even though the patient remains asymptomatic. Steen et al [21], in an important cohort of 953 early cases of diffuse SSc, report that 16% of the patients have severe ILD, defined by a FVC < 55%.

Independently of the type of cutaneous disease, the presence of anti-Scl 70 (anti-topoisomerase 1) antibodies is correlated with an important risk of developing ILD, while the presence of anti-centromere antibodies is inversely correlated with the development of a severe form of ILD.

Clinically, ILD in SSc is often asymptomatic. The interstitial infiltration expresses itself by non-specific symptoms, often at a late stage when the pulmonary involvement is advanced. A systematic history may identify a dry cough, dyspnœa of effort, often ignored by the patient or masked.
by joint and/or muscular limitation on exercise, and general weakness. The physical examination reveals “Velcro” crepitations at both bases. Clubbing is exceptional. Interpretation of the respiratory signs should take account of the presence of diffuse cutaneous involvement of the trunk or muscular weakness that could limit alveolar ventilation. The presence of pulmonary arterial hypertension may also contribute to the development of dyspnoea. At a late stage of ILD cyanosis and signs of right heart failure may be found.

- The ILD remains asymptomatic for a long time.
- High resolution CT scanning allows an earlier diagnosis than a simple chest x-ray.
- ILD develops most frequently in diffuse cutaneous SSc, in the course of which it is often earlier and more severe.
- The presence of anti-topoisomerase 1 antibodies is also a risk factor for ILD.
- Pulmonary symptoms, when they develop, are non-specific.
- Diffuse cutaneous involvement of the trunk or muscular involvement may, themselves, cause alveolar hypoventilation.

Complementary investigations

The poor prognosis of ILD in the course of SSc is an indication for systematic screening. The rarity of the condition and the absence of factors predictive of survival or of progression of the pulmonary fibrosis explain the absence of precise consensus guidelines on screening examinations and the frequency with which they should be repeated. Nevertheless, it is now recognised that performance of a high resolution CT scan (HRCT), pulmonary function tests (PFT) with measurement of carbon monoxide transfer (DLCO), a six minute walk, with measurement of oxygen saturation by a frontal electrode on account of Raynaud’s syndrome, and an estimation of dyspnoea with the help of a Borg index are essential at the time diagnosis of SSc.

Biologically, 90% of SSc patients have anti-nuclear antibodies [22]. Among the antibodies specific to SSc, the anti-topoisomerase 1 (Scl-70) found in 20-40% of patients, is more often present in the diffuse forms of the disease and in association with ILD, while the anti-centromere antibodies are more often associated with the limited cutaneous forms and are rarely present in patients with ILD. The search for antinuclear antibodies should be undertaken in the presence of an undetermined diffuse ILD in a search for connective tissue disease and particularly SSc.

HRCT is a very sensitive examination (90-100%) and specific for the detection of ILD associated with SSc. It allows a non-invasive and reproducible analysis of the type of pulmonary lesions and their extent. HRCT allows detection of hyperdense pulmonary nodules and ground glass, which are associated with reticular opacities, and sometimes traction bronchiectasis (fig. 2a) [23]. The appearance most commonly found in NSIP is of ground glass, sometimes associated with honeycomb cavities in the mid-zones. These lesions are bilateral, symmetrical and predominantly basal and sub-pleural. On the contrary, in the rare cases of UIP the honeycombing is usually the predominant lesion (fig. 2b) [23].

Pulmonary involvement other than ILD have been described in SSc: bronchial thickening, bronchial dilatation as well as aspiration pneumonitis. The presence of isolated ground glass shadowing should raise the possibility of left heart failure.
The presence of ILD on the scan is not always an indication of clinically important ILD. The severity of the functional disturbance may be very variable during the evolution of SSc. Many patients who present with limited pulmonary fibrosis on HRCT usually remain stable during the course of follow up in the absence of any specific treatment. In idiopathic pulmonary fibrosis, and also in SSc, some authors have defined global lesion scores taking account of both the type and extent of the lesions. These scores have been correlated with the results of PFT. Above a score of 10, 100% of patients have abnormalities of TLC and DLCO, in other words, clinically significant pulmonary fibrosis. Between 7 and 10, the specificity is 83% and the sensitivity 60%. The appearance of, or increase in, the signs of pulmonary fibrosis between two successive examinations is the principal sign of progression. This is identified when minor signs of architectural distortion like scarring or major signs like honeycomb damage or fibrotic masses appear. The prognostic factors have not been well documented but some studies show that HRCT has a distinct predictive value in evaluating the inflammatory and fibrotic components, thus helping to predict the response to treatment.

Some authors have studied the sensitivity of HRCT for determining the presence of an alveolitis as well as its concordance with broncho-alveolar lavage (BAL) in the same patient. The presence of ground glass on HRCT is correlated with the alveolitis on the lung biopsy while the presence of reticulo-nodular lesions is predictive of little alveolitis and predominant fibrotic lesions. Clements et al suggest that the specificity of HRCT for the detection of alveolitis in the early stages of SSc will be increased by taking account of radiological abnormalities of the lobes used for BAL.

As in the case of idiopathic pulmonary fibrosis, PFT with measurement of DLCO should be undertaken routinely as a screening for early ILD. It is important to mention that the measurement of arterial oxygen saturation will be best performed with a frontal electrode. Digital and aural electrodes do not allow reliable measurement of saturation in patients with severe Raynaud’s syndrome.

The role of PFT is above all diagnostic, but they also allow determination of the clinical impact of the interstitial lung disease by accurately evaluating its severity. They provide prognostic information and allow assessment of the response to treatment. Pulmonary involvement is defined by a TLC and/or FVC less than 80% and/or a DLCO less than 75%. The functional profile shows a restrictive defect of variable severity associated with an alteration of alveolar-capillary function and hypoxaemia on exercise. This is often less marked than in idiopathic pulmonary fibrosis. A modest obstructive element, in the absence of a smoking history, may be found in a minority of patients. The presence of an early reduction in FVC is, for many authors, the most important risk factor for progression in ILD.

Few surgical lung biopsies are performed during the course of ILD in SSc on account of the invasive character and the lack of practical consequences of a precise histological diagnosis. Histologically, when biopsy is performed, the ILD in SSc most often shows the appearances of NSIP (fig. 3a) [24]. These consist of lesions at the same stage of evolution, where...
inflammatory infiltrates, without much destruction, predominate and fibrotic lesions are less marked. Less frequently UIP may be seen, with heterogeneous lesions at different stages of evolution and the presence of centres of young fibroblastic tissue (fig. 3b). Sometimes an appearance of OP or even DAD may be seen [24, 25]. In the study of Bouros et al, which included 80 patients with SSc and ILD with surgical biopsies, there was no correlation between the severity of the histological lesions and the progression of the ILD [24]. Thus there is no benefit from performing lung biopsies by video-thoracoscopy or thoracotomy in patients with SSc and ILD except in the case of discordance between the clinical progress and the radiological appearances.

In idiopathic pulmonary fibrosis the BAL constitutes one of the 4 major diagnostic criteria in the absence of a lung biopsy [12]. In the ILD of SSc the BAL is not specific but it shows an inflammatory alveolitis. This is defined by an overall increase in cellularity, with neutrophils over 3% and eosinophils over 2% of the total. As in idiopathic pulmonary fibrosis BAL does not allow determination of the histopathological type. In SSc Silver et al [26] were the first to suggest the existence of a correlation between evidence of inflammation in the BAL and impairment of the PFT. Thus evidence of an alveolitis is negatively correlated with stability or improvement in FVC and DLCO. Clements et al underlined the unreliable nature of BAL by showing a great variability in the degree of alveolitis in different lobes. To limit interpretation bias they propose performing BAL in two different lobes (the lower lobe and the middle lobe or lingula). The discovery of an alveolar hypereosinophilia is a bad prognostic sign and associated with reduced survival. BAL should also be used in case of rapid deterioration of ILD to eliminate bacterial or parasitic infection which constitute the principal differential diagnosis in this situation.

What is the place of BAL in the follow up of ILD associated with SSc? Silver et al [26] were the first to suggest that the presence of an alveolitis, with an increase in neutrophils and eosinophils in the BAL, is associated with a decline in lung function. Subsequently White et al [27] reported in a retrospective study of 103 sclerodermic patients, followed for an average period of 16 months, that the presence of an alveolitis is not necessary or sufficient to predict or confirm progression of the ILD. In fact, in this study, 25% of the patients had a significant reduction in FVC and 40% had a significant reduction in DLCO in the absence of an alveolitis. Conversely, they found, in this study, that one quarter of the patients with alveolitis had stable PFT during the course of follow up.

Thus, the diagnostic management and follow up of ILD in the course of SSc should rely on HRCT and PFT. BAL should not be performed routinely but rather in case of diagnostic uncertainty. In the case of progression it should be performed readily if there is uncertainty between progression of the disease or an infective complication.

• High resolution CT scanning, PFT with measurement of DLCO, a 6 minute walking test with measurement of SaO₂, by a frontal electrode and an estimation of dyspnoea with the help of a Borg index are indispensable in the initial investigation of SSc.
• In idiopathic pulmonary fibrosis and in SSc global lesion scores have been defined, taking account of both the type and extent of the lesions, and these scores are correlated with the results of the PFT.
• An appearance of ground glass on the HRCT is correlated with the presence of alveolitis in the lung biopsy, while reticulo-nodular lesions indicate the presence of fibrosis.
• The PFT are of diagnostic, functional and prognostic importance.

Prognosis

The prognosis of ILD in SSc is better than that of idiopathic pulmonary fibrosis [17]. Black and Asiatic race, male sex, cardiac involvement and the early stages of SSc are more often associated with a severe form of ILD according to some authors but these data have not been confirmed in other studies.

The main factors defining the prognosis of ILD associated with SSc are an onset that is severe in terms of clinical criteria (dyspnoea, crackles), respiratory function (DLCO and/or FVC<70%) and HRCT (extensive lesions or predominant ground glass); or rapidly progressive ILD defined by a loss of FVC of 10% or DLCO of 15%) within one year [21]. For the majority of authors the data from BAL do not influence the therapeutic decisions. Nevertheless, in the study of Bouros et al, a proportion of eosinophils of over 5% in the BAL was a bad prognostic factor [24].

The histological type of ILD has not been shown to be of prognostic value. In the same study, no correlation was found between histological type and survival, as opposed to the DLCO and eosinophils >5%.

In practice, it is necessary to follow the progress of the ILD by performing PFT every 6 months, or more frequently in case of clinical deterioration noticed by the patient, in the absence of another cause such as a pulmonary arterial hypertension or infection. Thus rapid progression and significant subacute exacerbations may develop in the course of ILD in SSc and their early detection could improve the therapeutic management. The survival of patients with ILD in the course of SSc is variable. At 5 years, including all types, it is 85% [16]. In the diffuse forms of the disease, with all causes of death included, the 9 year survival of patients with ILD is 38%. In total, 12% of patients with ILD develop severe, chronic, respiratory failure [21].

Finally, it seems that patients with scleroderma and pulmonary fibrosis may be exposed to an increased risk of developing bronchial carcinoma, usually adenocarcinoma or broncho-alveolar carcinoma, though this remains controversial.
The prognosis of ILD in SSc is better than that of idiopathic pulmonary fibrosis.
The principal prognostic factors in ILD associated with SSc are ILD that is severe at its onset or a rapidly progressive ILD defined by a loss of 10% of FVC or 15% of DLCO over one year.
The interest of BAL is limited to differential diagnosis.
Six monthly PFT allow follow up of the progress of the ILD.
The 9 year survival in cases of ILD is 38% and 12% of the patients develop severe chronic respiratory failure.
The risk of bronchial carcinoma seems to be increased in cases of SSc associated with pulmonary fibrosis.

Treatment

It is important to mention that symptomatic treatment including oxygen therapy, pulmonary rehabilitation and treatment of gastro-oesophageal reflux are very important in the management of ILD in SSc.

Anti-fibrosing agents

Many anti-fibrosing treatments have been evaluated in the course of ILD in SSc without one of them proven to be effective in a prospective randomised, placebo controlled trial [28]. D-penicillamine (DP), or 2-amino-3-mercaptovaline, has been recommended since the early 1970’s for the treatment of SSc, giving some improvement in the cutaneous involvement. Only one retrospective study has provided evidence of an improvement in survival in patients with pulmonary fibrosis [29]. However, the use of DP is severely limited by its numerous side effects: proteinuria, digestive symptoms, cytopenia, induction of auto-immune disorders and obliteratorive bronchiolitis (particularly dangerous in the context of ILD) [30], and a recent randomised double blind trial has shown evidence that the doses of DP classically used (750-1000 mg/day) are no more effective, and induce more side effects, than smaller doses (125mg alternate days for 2 years) [31]. These data throw doubt on the possible effectiveness of DP in the treatment of SSc.

Interferon gamma (IFN-γ), the most powerful inhibitor of collagen synthesis by fibroblasts [32], particularly in SSc patients [33], has been proposed as a treatment for SSc and 6 open studies have been reported since 1989 [34-39]. Four of them reported a benefit on the skin [35-39], one reported a benefit on the skin and oesophageal and joint symptoms [34], while in one study no beneficial effect was observed [38]. In the one prospective randomised trial available, only the skin involvement was improved by INF-γ [39]. One prospective randomised trial has evaluated interferon alpha-2b (INF-α) in SSc; no benefit was found and in one case deterioration of the pulmonary disease was seen [40].

Immunosuppressants

Immunosuppressants were evaluated at the end of the 1980’s and no benefit was found with 5-FU or chlorambucil in randomised, prospective, placebo controlled trials [41, 42]. In 1993 Silver et al [43] reported that patients with ILD associated with SSc and receiving oral cyclophosphamide (CYC) had stable respiratory function tests. Since that time other retrospective studies have found evidence of a beneficial effect of oral CYC in the treatment of ILD in SSc [63], leading to an improvement in PFT and/or HRCT after one year [27, 44-49]. In 2000, White et al [27] confirmed these findings in a retrospective study of 103 patients with ILD with an average remission of 16 months. The patients were divided into three groups: 39 with alveolitis on the BAL and treated with CYC, 30 with alveolitis on the BAL but not treated and finally 34 patients without alveolitis and not treated. The authors observed a deterioration of lung function and an increase in mortality in the patients with alveolitis and not receiving CYC compared to those who received treatment [27]. 72% of the patients with alveolitis who were treated either stabilised or improved their FVC after treatment with CYC. Since that time there has also been evidence from retrospective studies that intravenous CYC improves the PFT of SSc patients with ILD [46, 48, 50-56], possibly in combination with corticosteroid therapy [43, 51, 54].

The results of two randomised therapeutic trials have been reported recently. The “Scleroderma Lung Study”, a prospective, randomised, placebo controlled study, included 162 patients of whom 142 were able to be evaluated after one year [57]. A minimal benefit on FVC was found in the group treated with CYC (p<0.03) [57]. Thus, at 12 months, the difference in FVC between the CYC group and the placebo group was 2.53% in favour of the CYC group. There was no difference for DLCO. At two years, the difference between the two groups was not significant. The “Fibrosing Alveolitis in Scleroderma Trial” (FAST) included 45 patients with ILD and SSc who were randomised to an arm receiving prednisolone (20mg/day) and 6 monthly boluses of CYC (600mg/m²) or placebo. The patients in the CYC arm showed no significant improvement in FVC at one year compared to those receiving the placebo with a difference of −4.76% (p=0.08) [58]. Thus these two trials have not shown evidence of more than a minimal benefit of CYC compared to placebo [57, 58].

Nevertheless, with exception of the trial of Silver et al [43] in 1993, in which 9/14 patients showed a fall in PFT in the 3 to 24 months prior to their entry into the study, none of the studies reported in a search of the literature included patients selected on the basis of recent progression of the ILD. This probably explains the difficulty of showing a clinically relevant beneficial effect of CYC in scleroderemic patients with ILD. We have recently undertaken an open study including 29 SSc patients with rapidly progressing
ILD (loss of 10% of FVC or of 15% of DLCO) in the 12 months preceding treatment with CYC. The patients received six boluses of CYC alternating with oral azathioprine in a dose of 2-3mg/kg. The patients, who had had an average decline in FVC of 19% during the year preceding the beginning of treatment, were stable after 6 months and two years of treatment [59].

Intensive treatment with high dose chemotherapy and autograft with peripheral stem cells (PSC) has been proposed for several years for the treatment of auto-immune disorders refractory to conventional treatments [60, 61]. In a recent update, Tyndall reported 55 SSc patients treated by autograft with PSC with an average remission of 12 months. The mortality of the procedure was 17%. Seventy percent of the patients had an improvement > 25% of their skin lesion score and stabilised PFT [62]. Among the eight patients treated by PSC graft reported by Furst et al [63], two, who had received excessive pulmonary irradiation during total body irradiation (TBI), died from interstitial pneumonia. An improvement in skin lesions and stability of ventilatory function was seen in all the survivors. The mortality level of patients treated by autograft of PSC seems to have improved in more recently reported series.

Among the other treatments without demonstrated effectiveness which may be considered are azathioprine (AZA) [64] and the mycophenolate mofetil [65]. Very few data are available in the literature concerning the use of AZA in the treatment of SSc. One study based on 19 patients reported in 1979 seemed to show that AZA (2-2.5mg/kg/day) could, in some patients, control the progression of SSc [64].

In a prospective randomised study, 30 patients with SSc received oral CYC (2mg/kg/day for 1 year and then 1mg/kg/day) and 30 patients received oral AZA (2.5mg/kg/day for 1 year then maintained at 2mg/kg/day) for 18 months. All the patients received prednisone more than 15 mg/day, progressively reduced and then stopped after 6 months. At the end of the study the Rodnan cutaneous score, the incidence of Raynaud’s syndrome and the ESR were improved in the group treated with CYC whereas the FVC and DLCO did not change in the group treated with CYC but deteriorated in the group treated with AZA [49].

Corticosteroids are used in SSc for their anti-inflammatory and immuno-suppressive properties, but also have an anti-fibrosing effect by reducing the synthesis of the mucopoly-saccharides necessary for the formation of collagen [66]. Some authors have also recommended this treatment for the alveolitis of SSc [67] by analogy with that proposed for idiopathic pulmonary fibrosis [68-70]. Nevertheless, in SSc patients, in addition to their classical side effects, corticosteroids prescribed at a dose of >15mg/day have been incriminated in the development of acute renal failure [70].

Nevertheless AZA alternating with boluses of CYC could be suggested for the treatment of episodes of interstitial pulmonary disease [71].

In patients where the disease progresses despite CYC, single lung transplantation may be considered if there is no other visceral involvement or digital ulceration. The survival at two years of SSc patients subjected to lung transplantation is identical to those receiving a lung transplant for idiopathic pulmonary fibrosis.

- The efficacy of interferons, 5-FU or chlorambucil has not been established.
- Among the immunosuppressants, cyclophosphamide appears to be the most effective.
- Azathioprine and the mycophenylate mofetil may be used even though there are very few data in the setting of ILD in SSc.
- A lung transplant may be considered in cases of severe ILD progressing despite. CYC if there is no other visceral involvement and no digital ulceration.

### Conclusion

The ILD of SSc is most often slowly progressive. However, in a small proportion of cases it may progress rapidly to respiratory failure and today it constitutes one of the two main causes of death in SSc. Routine monitoring of PFT is a key element in the detection of rapid progression of the disease and should allow the initiation of immunosuppressant treatment with the minimum delay.

### Acknowledgements

This work was undertaken with the support of the Association of French Scleroderms. Luc Mouthon, Alice Berezne and Loïc Guillemin are members of the French Scleroderma Research Group (GFRS).

### LEARNING POINTS

- Systemic sclerosis (SSc) is a generalised disease of connective tissue, the arterioles and the microvasculature.
- Pulmonary involvement is common in the course of SSc.
- One should consider the diagnosis of SSc in the presence of sclerotic lesions extending above the metacarpo-phalangeal joints, or in the case of pulmonary fibrosis a basal predominance, sclerodactyly, and scarring or loss of tissue of the pulps of the fingers.
- The prevalence of diffuse infiltrative lung disease in the course of SSc varies according to the studies from 16-100% of cases.
ILD develops mainly in the course of the evolution of diffuse cutaneous SSc, much less often in the limited cutaneous forms.

The principal complementary investigations are HRCT and PFT.

BAL and biopsies are little used.

The main prognostic factors in ILD associated with SSCs are a severe onset with dyspnoea, crepitations, a DLCO and/or FVC <70% and extensive lesions on the scan as well as rapid progression.

Treatment rests mainly on immunosuppressants, particularly cyclophosphamide.

References


69 Steen VD, Medsger TA. Case-control study of corticosteroids and other drugs that either precipitate or protect from the development of scleroderma renal crisis. *Arthr Rheum* 1998; 41: 1613-9.