The scleroderma lung: where do we stand?

Silvia Bellando Randone & Marco Matucci Cerinic

Dept of Experimental and Clinical Medicine
Division of Rheumatology
University of Florence
The scleroderma lung: where do we stand?

1. ILD & PAH
2. Lung in early disease
3. Risk factors
4. Diagnosis and screening: HRCT chest, DLCO, Lung ultrasound
5. Biomarkers
6. Treatment
7. Conclusions
Systemic Sclerosis

- Pathological similarities with other CTDs
- Complex pathology
- Patients exhibit features of >1 disease
- Rare disease
- Shares clinical manifestations with other CTDs
- Heterogeneous disease

CTD = connective tissue disease

The disease evolution

- **Limited SSc**
  - Pulmonary hypert., malabsorption

- **Diffuse SSc**
  - Lung, heart, GI, kidney

**Skin thickness**

**Disease duration (years)**

2, 5, 10, 20

**References**

Medsger T & Steen V, Systemic Sclerosis, 1995, p 51, Williams & Wilkins
1. Interstitial Lung Disease (ILD) & Pulmonary arterial hypertension (PAH)

...the most pressing challenges associated with ILD are how best to define, diagnose, and treat CTD-ILD disorders with potentially substantial morbidity and mortality...

A Fischer & R Du Bois  Lancet 2012;380:691

ILD:
- 90% of SSc patients
- 33% of the deaths
- From 40 to 75% of SSc patients demonstrate abnormal pulmonary function tests
- 42% of patients with SSc-ILD will die of disease progression within 10 y diagnosis

PAH
- prevalence depends on the method of detection
- 13-35% of SSc patients, 9.2% of lcSSc and 5.8% of dcSSc patients
- around 28% of the deaths
Differential diagnosis of “PH” SSc

- Pulmonary arterial hypertension (PAH)
- Interstitial lung disease (ILD)
- Chronic thromboembolic pulmonary hypertension (CTEPH)
- Others
- Pulmonary veno-occlusive disorder (PVOD)
- Myocardial involvement

PH = pulmonary hypertension
Changes in causes of SSc-related deaths over time

- Scleroderma renal crisis
- PAH
- Interstitial lung disease

courtesy of Virginia Steen.
2. ILD in *early* and *very early* SSc

Early systemic sclerosis: assessment of clinical and pre-clinical organ involvement in patients with different disease features

Valentini G. et al., Rheumatology 2011

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Prevalence of functional cardiac, lung and oesophageal alterations in 115 RP patients subdivided into three groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early SSc</td>
</tr>
<tr>
<td>E:A ratio &lt;1°</td>
<td>1/19</td>
</tr>
<tr>
<td>FVC &lt;80%</td>
<td>0</td>
</tr>
<tr>
<td>DLCO &lt;80%</td>
<td>7/19</td>
</tr>
<tr>
<td>DLCO &lt;70%</td>
<td>5/19</td>
</tr>
<tr>
<td>Basal LES pressure &lt;15 mmHg</td>
<td>4/18</td>
</tr>
<tr>
<td>Plus distal oesophageal hypomotility</td>
<td>0/4</td>
</tr>
</tbody>
</table>

°Not alternatively explained. P1: early vs probable SSc; P2: early SSc vs UCTD; P3: probable SSc vs UCTD.
Treat or not to treat ILD? This is the question

The goal is to achieve and maintain remission of lung disease, thereby stopping its progression

- Who treat?
- When?
- What drugs to use?
Treat or not to treat ILD? This is the question

- Who treat?

Patients with a higher risk to develop severe ILD considering the pros and cons of immunosuppressive therapy, the patient's age and possible desire to get pregnant.
3. Risk factors for severe ILD

- Male sex,
- black race,
- older age,
- early disease, seropositivity for anti-topo I antibodies
- a decreased FVC in the first years
- serial pulmonary function tests (PFTs) that decrease by greater than 10%

A reduction in DLCO: early sign of pulmonary disease in SSc, as well as an important predictor of mortality

A loss of capillary density on videocapillaroscopy

worse FVC and DLCO
Predictors of mortality and progression in scleroderma-associated interstitial lung disease: a systematic review.

Winstone TA Chest 2014

- male sex,
- *extension of disease on high-resolution CT (HRCT) scan*,
- presence of honeycombing,
- *elevated* Krebs von den Lungen (*KL-6*) *values*,
- increased alveolar epithelial permeability

as *predictors of both mortality and ILD progression*
Patients with more than 20% HRCT abnormalities: extensive lung disease
Patients with less than 20%: limited lung disease.
If HRCT evaluation was inconclusive patients were considered affected by extensive lung disease if FVC<70% and by limited lung disease if FVC≥70%.

Patients with extensive lung disease had strikingly higher mortality and faster deterioration of lung function.
Treat or not To treat ILD? This is the question

➢ When?

"the risk of progression of SSc-ILD is highest in the first 5 years of systemic disease, and especially in the first 2 years"

V. Steen, Ann Rheum Dis 2003

An early diagnosis of lung involvement is mandatory!!
4. Diagnosis & screening

HRCT chest: **diagnostic «gold standard»**

- To early detect ILD in patients even from the subclinical stages to potentially help guide management
- To characterize the pattern of fibrosis: NSIP (the most common), UIP
- To assess extent of fibrosis: predicts disease course, mortality and treatment response

**Ground glass** hazy increase in lung parenchymal opacity with preservation of bronchial and vascular markings

**Lung Fibrosis** presence of interlobular septal thickening, intralobular septal thickening, traction bronchiectasis, and bronchiolectasis

**Honeycombing** clustered air-filled cysts with well-defined walls

![HRCT images](image-url)
Significance of Ground-glass Opacity on HRCT in Long-term Follow-up of Patients With Systemic Sclerosis

Shah MR et al, 2007 J Thorac Imaging

Only 5% of SSc patients with GGOs and non fibrotic interstitial opacities shows an improvement of HRCT findings over a mean follow-up period of 27 months.

In SSc, groundglass opacity is most commonly associated with irreversible disease.

Disease progression or improvement could not be predicted by the presence of ground-glass opacity.
Coronal and axial HRCT images for patients with mild quantitative extent of lung fibrosis (QLFib) and interstitial lung disease (QILD) (A) and severe extent of fibrosis and ILD (B).

Scatter plots of bivariate correlations between the single best variable from the one-variable best set model and extent of lung fibrosis (QLFib) in the zone of maximal involvement (ZM) in SLS I and II (A and C, respectively) and in the whole lung (WL) in SLS I and II (B and D, respectively).

**DLCO provides the best overall estimate of HRCT-measured lung disease**
HRCT chest: «gold standard» but...

- CT uses ionising radiation, which has been linked to an increased cancer risk, in particular non-Hodgkin’s lymphoma, lung, breast and liver cancer.

- SSc patients are often screened annually

A reduction of radiation dose is a crucial!
Unnecessary radiation exposure from medical imaging in the rheumatology patient

Our responsibility to change

Our rheumatology patients, often young at disease onset and female, are therefore especially sensitive to radiation damage. The chronic nature of most rheumatic diseases also makes our patients more vulnerable to the cumulative effects of serial testing, as we monitor the course of disease and response to therapy.
Rheumatological patients are much more often women (with a 4:1 ratio), who are 38% more vulnerable to radiation than men. The age at first diagnosis is on average relatively young, and radiation vulnerability increases with younger age, being twice as high at 30 years than at 50 years of age. Data suggest a particular sensitivity of DNA from rheumatology patients, with defective repair ability. Rheumatological patients frequently use alkylating agents such as methotrexate and cyclophosphamide that are known biological modifiers of radiation-induced DNA damage. Any radiation dose administered, that has not been considered carefully with risk–benefit analysis, is unacceptable.
Diagnosis & screening: new tools

1. Screening for interstitial lung disease in systemic sclerosis: performance of high-resolution CT with limited number of slices: a prospective study
   Frauenfelder T et al, ARD 2014

2. Ultrasound lung comets in systemic sclerosis: a chest sonography hallmark of pulmonary interstitial fibrosis
   Gargani L., Rheumatology 2009


4. Comparison of a new, modified lung ultrasonography technique with high-resolution CT in the diagnosis of the alveolo-interstitial syndrome of systemic scleroderma
   Mohammadi A. et al, Med Ultrason 2014
Screening for interstitial lung disease in systemic sclerosis: performance of high-resolution CT with limited number of slices: a prospective study
Frauenfelder T et al, ARD 2014

One image apical, one at the level of the carina and six images at the basal level with 1 mm slices, the upper three images with an increment of 80 mm, the basal six images with an increment of 15 mm.

HRCT image series with low sampling rate allow an accurate detection of ILD with very-low-radiation dose, making this approach potentially valuable for screening in patients with SSc.

<table>
<thead>
<tr>
<th>Table 2 Estimated accuracy and diagnostic certainty in detecting ILD on reduced HRCT scans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reader 1</td>
</tr>
<tr>
<td>-----------------------------</td>
</tr>
<tr>
<td>Sensitivity (95% CI)</td>
</tr>
<tr>
<td>Specificity (95% CI)</td>
</tr>
<tr>
<td>Accuracy</td>
</tr>
<tr>
<td>NPV (95% CI)</td>
</tr>
<tr>
<td>High diagnostic confidence*</td>
</tr>
</tbody>
</table>

*Degree of confidence score 1 or 2 (i.e. 1=fully confident; 2=probably confident).
HRCT, high-resolution CT; ILD, interstitial lung disease; NPV, negative predictive value.
Lung ultrasound (US)

- A non-invasive method with no risk of radiation exposure.

- The ultrasonographic feature of pulmonary fibrosis consists of detection and quantification of the US lung comet tail sign (B-line artifacts). This sign is generated by the reflection of the US beam from the thickened subpleural-interlobar septum.

- The validity of lung US has been demonstrated by comparing this new technique with CT.
Ultrasound lung comets in systemic sclerosis: a chest sonography hallmark of pulmonary interstitial fibrosis  

Gargani et al, Rhetmatology 2009

**FIG. 2.** Correlation between ULC number and Warrick score in identifying pulmonary interstitial fibrosis.

ULCs are more frequent in the dSSc than in the ISSc form and are reasonably well correlated with HRCT-derived assessment of lung fibrosis.
The presence of B-lines at LUS examination correlates with ILD at HRCT. LUS is very sensitive for detecting ILD even in patients with a diagnosis of very early SSc. The use of LUS as a screening tool for ILD may be feasible to guide further investigation with HRCT.
Comparison of a new, modified lung ultrasonography technique with high-resolution CT in the diagnosis of the alveolo-interstitial syndrome of systemic scleroderma

Mohammadi A., Med Ultrason 2014

a) The comet tail sign (2 B-lines) in the mild form of alveolo-interstitial involvement in systemic sclerosis. b) HRCT showing the mild form of alveolo-interstitial involvement in systemic sclerosis (Warrick score=4).

a) The comet tail sign (4 B-lines) in moderate form of alveolo-interstitial involvement in systemic sclerosis. b) HRCT showing moderate form of alveolo-interstitial involvement in systemic sclerosis (Warrick score=14).

Also modified lung US assessment shows a good correlation with HRCT findings
5. Biomarkers

- chitinase
- tenascin C
- growth differentiation protein 15
- the alveolar epithelial cell antigen, KL-6
- chemokine CXCL4
- Serum IL-6 levels

all correlate with the presence of SSc-ILD
Chitinase 1 is a biomarker for and therapeutic target in scleroderma-associated interstitial lung disease that augments TGF-β1 signaling. Lee CG et al, J Immunol 2012

Chit1 expression is increased in SSc patients with ILD and correlates inversely with lung function.
A, Significantly increased serum tenascin-C (TN-C) levels in systemic sclerosis (SSc) patients with pulmonary fibrosis (PF) compared with both SSc patients without pulmonary fibrosis and normal healthy individuals, as measured using an enzyme-linked immunosorbent assay. \( P \ 0.0001; \ P \ 0.009; \ P \ 1.1 \ 108. \\
B, Increased serum TN-C levels in SSc patients (n 4) after the development of pulmonary fibrosis (\( P \ 0.03))

The increased lung tissue levels of TN-C parallel the levels detected in the sera of SSc patients with pulmonary fibrosis, suggesting that TN-C may be a useful biomarker for SSc-related pulmonary fibrosis
GDF15, a marker of lung involvement in Systemic sclerosis, is involved in fibrosis development but does not impair fibrosis development.

Lambrecht S. et al. *Arthritis Rheum* 2013

- An elevated steady state of GDF15 serum levels correlate with extent of organ involvement (skin and lung) and with a distorted lung function.
- The evolution of GDF15 serum levels within a patient during follow-up is highly associated with the course of disease.
- GDF15 is directly involved in the expression of proinflammatory cytokines and chemokines, such as IL6 and CCL2.
- GDF15 is rather a factor secreted upon fibrosis development participating in the initial inflammatory stages, but that is not essential for fibrosis development.

Determination of GDF15 serum levels may have potential as an aid to monitor disease activity.
**Surfactant Protein D and KL-6 as Serum Biomarkers of Interstitial Lung Disease in Patients with Scleroderma**

*Hant F.L. et al, 2009 The Journal of Rheumatology*

A. SP-D levels in SSc patients (with and without “alveolitis”) and healthy controls.
B. KL-6 levels in SSc patients (with and without “alveolitis”) and healthy controls.
C. SP-D levels in SSc patients with and without “alveolitis.”
D. KL-6 levels in SSc patients with and without “alveolitis.”

**Serum levels of SP-D and KL-6 appear to be indicative of “alveolitis” in SSc patients.**

**KL-6 levels are more strongly associated than SP-D with the HRCT-fibrosis score**

Bonella F. et al, Sarcoidosis Vasc Diffuse Lung Dis, 2011
Proteome-wide Analysis and CXCL4 as a Biomarker in Systemic Sclerosis


Patients with highest levels of CXCL4 had significantly earlier evidence of lung fibrosis, as measured by a relative decline of more than 30% in the FVC or by the presence of bilateral fibrosis on HRCT.

Levels of CXCL4 were elevated in patients with systemic sclerosis and correlated with the presence and progression of complications, such as lung fibrosis and PAH.
Serum Interleukin 6 Is Predictive of Early Functional Decline and Mortality in Interstitial Lung Disease Associated with Systemic Sclerosis De Lauretis A., J Rheumatol 2013

IL-6 was significantly predictive of DLCO deterioration in both IPF and SSc and IL6 values>7.67 pg/ml were predictive of risk of death within the first 30 months in patients with mild SSc-ILD

serum IL-6 levels appear to be predictive of early disease progression in patients with mild ILD
6. Treat or not To treat ILD? This is the question

➢ Which drugs to use?

• Non selective immunosuppressors (*CYC, AZA, MMF*)
• Immunoglobulins
• Hematopoietic stem cell transplantation
• Biological immunotherapies (*Rituximab, Tocilizumab? Abatacept? Alefacept, Basiliximab*)
• Lung transplantation
Is immunosuppressive therapy the anchor treatment to achieve remission in systemic sclerosis?

Cappelli S., Rheumatology 2014

The EULAR/EUSTAR recommendations for the management of SSc stated that cyclophosphamide “should be considered for the treatment of SSc-ILD”

Alkylating agents exhibit significant toxicities that must always be considered in the risk / benefit assessment.
Effects of 1-year treatment with cyclophosphamide on outcomes at 2 years in scleroderma lung disease.


- CYC is still the most used drug as induction treatment to achieve remission in ILD
- Results of the Scleroderma lung study I show that the beneficial effects of CYC persisted or increased for several months after stopping the therapy, but are no longer apparent after 12 months

maintenance treatment after CYC is needed
**Biological immunotherapies**

**Rituximab**
a chimeric monoclonal antibody directed against CD20, an antigen expressed on early pre-B and mature B cells.

**Basiliximab**
a monoclonal antibody that blocks the α chain of the IL-2 receptor (CD25) expressed on T cells, leading to the inhibition of their activation and proliferation.

**Alefacept**
a recombinant fusion protein inhibits the costimulatory interaction between APC and CD2 memory T effector cells.

**Tocilizumab**
humanised anti-IL-6 receptor antibody. The contribution of IL-6 to dermal fibrosis, but also to lung fibrosis, has been demonstrated in murine SSc mod.

**Abatacept**
a recombinant CTLA4Ig fusion protein that selectively modulates costimulation resulting in downregulation of T cell activation.

They report herein an improvement of lung function as indicated by a linear increase in PFTs, a modest improvement of HRCT findings and an improvement of mRSS following treatment with RTX during a 2-year period.
The comparison of RTX treated versus untreated matched-control SSc patients from the EUSTAR cohort demonstrated improvement of skin fibrosis and prevention of worsening lung fibrosis.
Tocilizumab

Treatment of systemic sclerosis with tocilizumab
Fernandes Das Neves et al. Rheumatology (Oxford) 2015

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patient</th>
<th>Baseline</th>
<th>6 months</th>
<th>9 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRSS</td>
<td>1</td>
<td>17</td>
<td>11</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>41</td>
<td>26</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>7</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Digital ulcers, n</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>8</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>1</td>
<td>35</td>
<td>47</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>49</td>
<td>57</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>70</td>
<td>82</td>
<td>-</td>
</tr>
<tr>
<td>Patient global assessment (0-100)</td>
<td>1</td>
<td>70</td>
<td>40</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>70</td>
<td>30</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>60</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>Haemoglobin, g/dl</td>
<td>1</td>
<td>9.5</td>
<td>11.5</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>11.8</td>
<td>13.3</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>14.2</td>
<td>14.7</td>
<td>-</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td>1</td>
<td>86</td>
<td>55</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>46</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>CRP, mg/dl</td>
<td>1</td>
<td>8.1</td>
<td>1.9</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1.75</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>DLCO, %</td>
<td>1</td>
<td>47.8</td>
<td>50</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>72.1</td>
<td>75</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>78</td>
<td>63</td>
<td>-</td>
</tr>
<tr>
<td>Chest CT (Wells’ score)</td>
<td>1</td>
<td>Global disease extent 40% Reticular 40% Ground glass 60%</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Global disease extent 15% Reticular 20% Ground glass 80%</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Global disease extent 20% Reticular 15% Ground glass 60%</td>
<td>Global disease extent 25% Reticular 15% Ground glass 85%</td>
<td></td>
</tr>
</tbody>
</table>

TCZ might be a valuable treatment for SSc. These results reinforce the need for clinical trials using TCZ in diffuse SSc.

There was a halt in the progression of lung disease in patient 1 (no progression on CT; DLCO 50%) and patient 2 (no progression on CT; DLCO 75%) and only a slight CT worsening and decrease in DLCO to 65% in patient 3.
Survival after lung transplantation in systemic sclerosis

Khan JY et al Resp Medecine 2013

The short-term and intermediate-term survival post-lung transplantation are similar to IPAH and ILD patients requiring lung transplantation.

Causes of death: graft failure, infection, cardiac events, hemorrhagic stroke, respiratory failure, malignancy, pulmonary hypertension, complications of bronchiolitis obliterans syndrome, anesthetic complication, and scleroderma renal crisis.
An early “diagnosis” and “treatment” of ILD is mandatory.

A diagnostic strategy with radiation-sparing approach is needed.

Biomarkers could be helpful in ILD management.

Biological immunotherapies are the new therapeutic frontiers.
6. Conclusions I

- ILD and PAH are the two major causes of morbidity and mortality in SSc patients.
- **HRCT chest is still the gold standard** for ILD diagnosis but can be substituted with HRCT limited number of slices.
- Lung-US can be particularly useful in monitoring of ILD-SSc but cannot replace HRCT.
- Further studies with larger populations are needed to define whether LUS could become the imaging screening technique for an early and sustainable detection of ILD in SSc.
- Regular monitoring of PFTs in SSc patients is especially important during the first 5 years.
- Biomarkers could be helpful in SS-c ILD management.
7. Conclusions II

- **The goal of ILD treatment is to achieve and maintain remission of lung disease**, thereby stopping its progression
- **Patients with a higher risk to develop severe ILD should be treated soon as possible**
- CYC is still the most used drug as induction treatment to achieve remission in ILD but **maintenance treatment after CYC is needed**
- Preliminary results on the efficacy of RTX for ILD results are encouraging and it can be consider as a valid treatment option in patients who do not tolerate CYC or with contraindication to it.
- TCZ might be a valuable treatment for SSc but clinical trials using TCZ in diffuse SSc are needed
- **The choice of treatment should always consider age, comorbidity, and in woman desire to get pregnant**
THANKS FOR YOUR ATTENTIONS