Current and Potential New Targets in Systemic Sclerosis Therapy:a New Hope

One year in review 2020: systemic sclerosis

DR E.JANDAGHI MD

Introduction

- Systemic sclerosis (SSc) is a connective tissue disorder characterised by:
  - ✓ immune dysregulation
  - ✓ endothelial cell dysfunction
  - ✓ defective vascular repair and neovascularization
  - ✓ progressive tissue fbrosis of the skin and internal organs ➡ increase morbidity and mortality

Introduction

- Myofibroblast that becomes 'activated' in response to a multitude of factors increased contractility and exuberant expression of collagen and fibronectin .
- This is conserved among whichever organ system is affected and is mainly the dermal and lung fibroblasts that are activated in SSc.
- Accumulation of fibrosis tissue and ECM in an organ defines fibrosis.
- around 45% of deaths in the Western world are attributed to a fibrosis component.
- The aim of this review is to give an overview of current perspectives on pathogenesis and new possible therapeutic targets in a disease that currently has an unmet need

Pathogenesis of SSc

- most signifcant genetic factors in the development of the disease:
- **HLA-DRB1 and HPB1**
- **non-HLA gene:**

  SNP: mutations in DGKQ → lung involvement

  mutations in PRR12 → cardiovascular events.

  vitamin D receptor gene polymorphism

  MIF (- 794 CATT7 and - 173*C) genetic variants

- **downregulation of LncRNA**, involved either in regulating genes engaged in tumour proliferation, or in tissue fibrosis and vascular alteration → possible link between the disease and cancer
- **different expression of miRNA**: (EGFL7) and miR- 126, miRNA-4484 and the matrix metalloproteinase (MMP)-21 , and miRNA-542-3p and 708-5p
- pathogenesis of SSc-ILD
- represent potential diagnostic biomarkers

Pathogenesis of SSc

- **A number of cytokines and chemokines have been linked to SSc and different disease expressions** :
- (IL)-1
- IL-6 levels were associated with the severity of symptoms and low resilience
- up-regulation of IL18, 17B, 17E
- CXCL4
- down-regulation of RNX3 :inversely correlated with skin involvement
- Lymphocyte T-related inducible ligand that competes for glycoprotein D binding to herpes virus entry mediator on T cells (LIGHT):
- ✓ early disease
- ✓ higher digital ulcers (DUs)
- ✓ creatine kinase elevation

Pathogenesis of SSc

- **Increased FcγRIIB expression on double negative memory B cells :**

  disease activity, presence of ILD, reduced lung function and heart involvement
- **reduction of efferocytosis capacity**
- **alteration of angiotensin I / angiotensin II / angiotensin-(1-7) axis**
- **environmental factors:**

  viruses (HHV6)

  heavy metals :

  aluminium, cadmium, mercury and lead identified in the blood and urine of SSc patients compared to controls, which may represent risk factors for SSc

Clinical manifestations and organ involvement

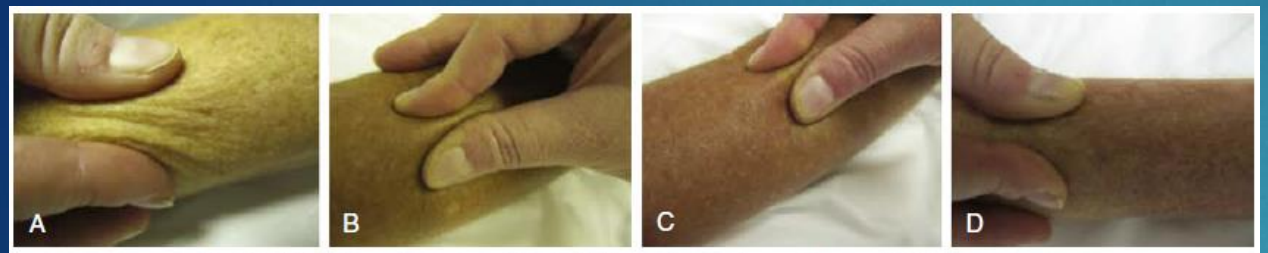
- **Becker *et al*. identifed :**

✓ age, active digital ulcer (DU), lung fibrosis ,muscle weakness and elevated C-reactive protein (CRP) level as predictors severe disease worsening (defned as organ failure within a period of 12±3 months) in dcSSc patients.

- **Another study recently supported**:

✓ the use of mRSS as an end point in clinical trials suggesting :

✓ fbrosis short-term progression (defned as an increase in mRSS >5 and ≥25% within 1 year) associated with long-term decline in lung function and worse survival with an increase of all-cause mortality in dcSSc



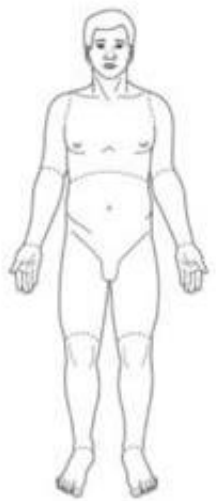
• **Fig. 89.8** Method used to semiquantify skin thickness in scleroderma. The modified Rodnan skin score is obtained by clinical palpation of 17 different body areas (fingers, hands, forearms, upper arms, chest, abdomen, thighs, lower legs, and feet) and subjective averaging of the thickness of each specific site: (A) 0 = normal; (B) 1 = mild; (C) 2 = moderate; and (D) 3 = severe. The maximum score is 51.

the grading is 0, normal skin; 1, thickened skin; 2, thickened and unable to pinch; and 3, thickened and unable to move.

Modified Rodnan Skin Score (MRSS) Document

Subject ID: _____

Date of Examination: _____



	Right				Left			
Fingers	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Hands	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Forearms	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Upper Arms	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Face			0☐	1☐	2☐	3☐		
Anterior Chest			0☐	1☐	2☐	3☐		
Abdomen			0☐	1☐	2☐	3☐		
Thighs	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Legs	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Feet	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Column Totals								
Total:								

Key: *0 – No Thickening* *1 – Mild Thickening* *2 – Moderate Thickening* *3 – Severe Thickening*

Notes:

Examiner:

Printed Name: _____

Signature: _____ Date: _____

Modified Rodnan skin score (mRSS

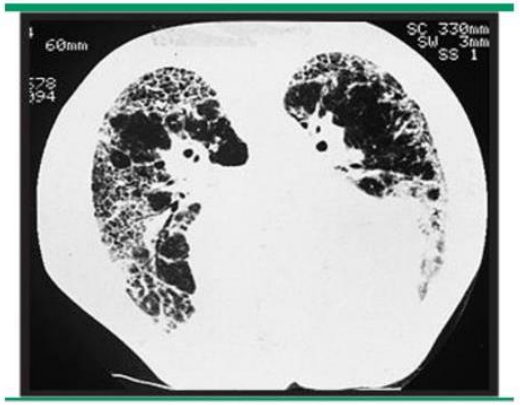
Clinical manifestations and organ involvement

- **In the last decades:**
  - the survival of SSc was improved and causes of death related to SSc-internal organ involvement have drastically changed.
  - The frequency of deaths due to scleroderma renal crisis (SRC) has signifcantly decreased since treatment for this has become possible
  - lung involvement (both ILD and pulmonary hypertension(PH)) represents the leading causes of morbidity and mortality in SSc

Clinical manifestations and organ involvement

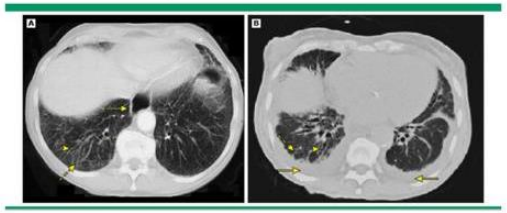
- **Pulmonary involvement in SSc:**
  - **A:most frequently presents as ILD:**
    - ✓ mainly: a non-specifc interstitial pneumonia(NSIP)
    - ✓ less commonly :usual interstitial pneumonia pattern (UIP)

Interstitial lung disease with honeycombing in scleroderma

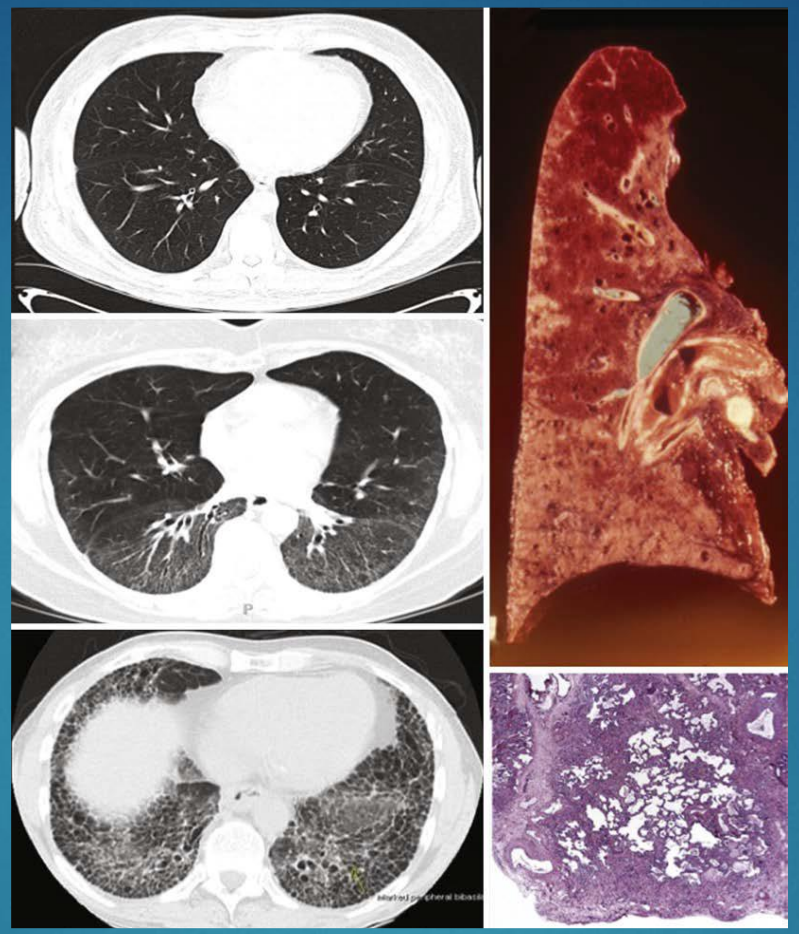


High resolution CT in a patient with scleroderma and interstital lung disease showing a reticular pattern, honeycombing, and traction bronchiectasis in both lung

CT of progressive interstitial lung disease in a patient with scleroderma



An axial CT scan through the base of the lungs (A) shows a reticular pattern (dashed arrow), early bronchiectasis (arrowhead), and a patulous esophagus (arrow). Image (B) is a CT scan performed 10 years later and shows progressive septal thickening (dashed arrow), bronchiectasis (arrowhead), and bilateral pleural effusions (arrows). The thickening of the bronchial walls suggests inflammation from recurrent aspiration.



Scleroderma-related interstitial lung disease: high-resolution chest CT scan showing (A) normalblung, (B) active alveolar inflammation (“ground glass” opacification), and (C) end-stage lung disease with honeycombing. (D) Gross pathology. (E) Histology showing fibrosing alveolitis.

Clinical manifestations and organ involvement

B.new pattern of ILD :

pleuroparenchymal fbroelastosis:

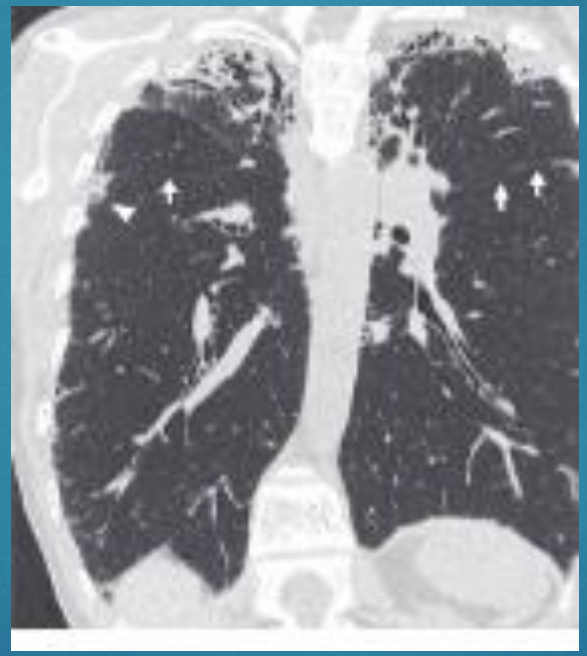
- defned as fbrotic thickening of the visceral pleura and subadjacent parenchymal areas of the upper lobes
- rare but characterised by negative prognosis

- patients with this pattern require a close, multidisciplinary follow-up.

❑characterized by:

✓PPFE is a slowly progressive disorder and its first symptom is dyspnea or dry cough.
✓ Chest pain because of pneumothorax
✓ slender with a flat rib cage or abnormally narrowed anterior–posterior thoracic dimension.
✓ Decreases in forced vital capacity, total lung capacity, and diffusing capacity are respiratory-function
✓ The most remarkable difference in clinical features between PPFE and IPF is imaging findings, with upper-lobe-predominant lesions in PPFE and lower-lobe-predominant lesions in IPF

Computed tomography (CT) through the lung apices demonstrating classical features of pleuroparenchymal fibroelastosis (PPFE), including pleural thickening, subpleural consolidation with coarse reticulation, and striking traction bronchiolectasis/bronchiectasis.



Clinical manifestations and organ involvement

C:Another distinct pulmonary manifestation in SSc

- **combined pulmonary fbrosis and emphysema (CPFE) syndrome**
- experienced more frequent unscheduled hospitalisations
- higher morbidity and mortality
- highly impaired lung function
- more frequently developed precapillary PH

Figure 1 CT scan of the chest of a 67-year-old female patient with combined pulmonary fibrosis and emphysema, showing centrilobular and paraseptal emphysema in the upper lobes (A and B), as well as ground-glass opacities, traction bronchiectasis, and honeycombing in the lower lobes (C and D). Note an aspergilloma in one of the paraseptal bullae in the right upper lobe (black arrow, in B

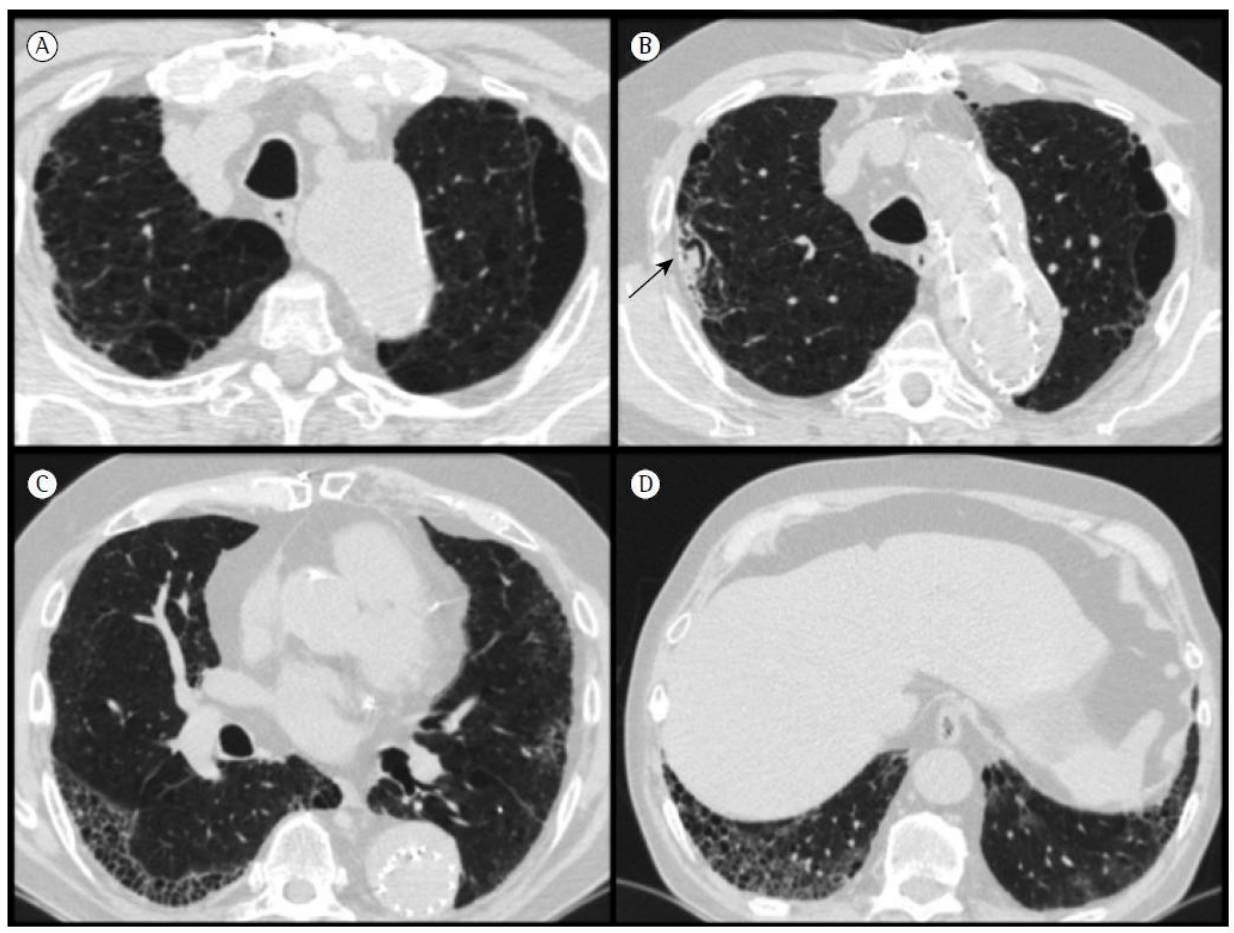
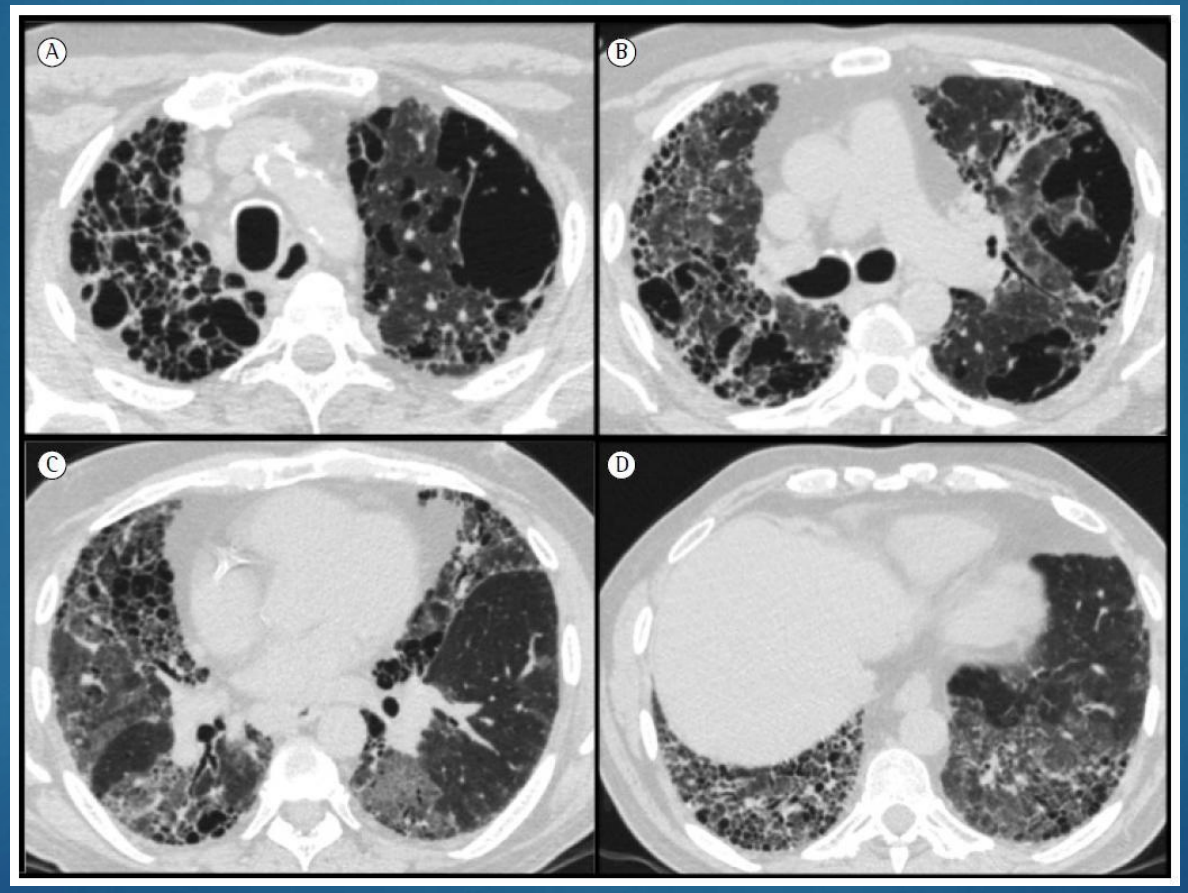


Figure 2 CT scan of the chest of a 70-year-old male patient with combined pulmonary fibrosis and emphysema and acute exacerbation of interstitial disease. Note predominantly paraseptal emphysema in the lung apices, with architectural destruction of the lung parenchyma (A and B). Extensive areas of ground-glass opacity and honeycombing can be seen in the lower lobes (C and D)



Clinical manifestations and organ involvement

D:small airway dysfunction

- Bonifazi *et al*. proposed using impulse oscillometry combined with HRCT to detect the dysfunctions of the small airways, which is not evaluable by PFTs.
- peripheral airways might bean early target of the SSc lung disease rather than a consequence of parenchymal architectural distortion
- interest has increased also in the use of the nitrogen single-breath washout test for early diagnosis of small airway involvement and for the assessment of ventilation distribution heterogeneity in SSc-ILD

Clinical manifestations and organ involvement

- identifcation of ILD:

✓ **Chest HRTC** is gold standard

✓ **lung ultrasound (LUS):**for early phases of the disease and in the follow up

- **ReyesLong *et al*. recently performed :**
- LUS in 68 SSc patients with respiratory involvement showing : positive correlation between the fndings of HRCT and LUS with a high sensitivity and specifcity (91.2% and 88.6%, respectively).
- The prevalence of ILD was 41.2% and the mRSS was associated with LUS and HRCT findings

Clinical manifestations and organ involvement

- **18F-FDG-PET/CT scan** :

morphologically‘positive’ GGO segments presented a clear 18F-FDG uptake, suggesting the existence of an increased metabolic activity of GGO, potentially due to inflammation

Clinical manifestations and organ involvement

- **nterestingly, a recent study enrolling 8013 lcSSc and 4786 dcSSc:**

- lcSSc-ILD may be progressive as in dcSSc subset and supports the inclusion of lcSSc patients in SSc-ILD trials as they may beneft from anti-ILD drugs
- recommended systematic screening and follow-up for lung involvement both in lcSSc and in dcSSc
- The presence of ILD or of initial fbrotic change may compromise gas exchange, however, SSc patients without detectable fbrosis may already present an alteration in gas transfer.

- impaired gas exchange is associated with alterations in pulmonary vascular morphology.

Clinical manifestations and organ involvement

- systolic pulmonary artery pressure (sPAP), vessel tree capacity and forced expiratory volume in frst second (FEV1%) were signifcant independent predictors of diffusing capacity for carbon monoxide (DLCOc%) predicted
- lung diffusing capacity for nitric oxide (DLNO): more sensitive in the detection of alveolar membrane diffusive conductance (DMCO) decrease than DLCO.
- DLNO and DLCO were signifcantly correlated with CT measurements of ILD

Clinical manifestations and organ involvement

- **A large, nationwide, population-based SSc study confrmed:**

- presence of ILD at baseline affects outcome in SSc
- all SSc patients should undergo screening for ILD (pulmonary function tests (PFTs) and HRTC) in order to diagnose ILD early.
- 50% of patients with SSc had ILD on HRCT and 46% displayed ILD progression defned as pulmonary function decline.
- Mortality correlated with the extent of lung fbrosis and was inversely related to baseline Forced Vital Capacity (FVC)%

Clinical manifestations and organ involvement

Pulmonary hypertension and pulmonary arterial hypertension

- ✓ PH and PAH together with ILD are the leading causes of mortality in SSc.
- ❖ **In a cohort of 93 patients with SSc-associated ILD:**
- ✓ 31.2% had RHC-proven coexisting PH,often occurs early after SSc diagnosis.
- ✓ diffuse subtype and had features of WHO Group III PH due to their ILD

Clinical manifestations and organ involvement

- **Last year a descriptive study of PH-related data from the multicentre RESCLE registry was carried out:**

- Estimated systolic pulmonary artery pressure (esPAP) was elevated (≥35 mmHg) in 43.3% of patients and this group was mostly dcSSc.
- the group with elevated esPAP presented a greater prevalence of anti-topoisomerase-1 antibodies compared to anticentromere antibodies and a higher rate of SRC was observed
- Early intervention and detection of PH associated with SSc may improve its prognosis.

Clinical manifestations and organ involvement

- **Ninagawa *et al.* recently proposed an algorithm to predict mean pulmonary arterial pressure (mPAP)>20 mmHg using non-invasive examinations in SSc patients by modifying the DETECT algorithm, with good sensitivity (87.5%) and specificity (92%).**
- elevation of FVC/ DLCO in pre- and early stages of SSc-PAH
- the weighting of FVC/DLCO
- the right axis deviation

may improve its predictability

Clinical manifestations and organ involvement

- **the first prospective study to assess and compare right ventricular output reserve and pulmonary arterial compliance (PAC; ratio of stroke volume to pulse pressure) in SSc patients with mildly elevated mean PAP, with normal mean PAP, and with manifest PH was performed:**
- screening of SSc patients by RHC at rest and during exercise may lead to an identification of early pulmonary vascular disease
- **Lindholm *et al.* reported:**
- Left ventricular (LV) peak global longitudinal strain (GLS) is decreased in SSc but it is not known whether low GLS is due to SSc or PAH
- low LV and right ventricular free wall GLS on cardiac MRI are indicative of increased mPAP and pulmonary vascular resistance (PVR)

non-invasive methods to select patients eligible for right heart catheterisation

Clinical manifestations and organ involvement

- ***Heart involvement :***

- Heart failure with preserved ejection fraction (HfpEF) is common in SSc and is associated with a worse prognosis

- NT-pro-BNP I increase (> 220 pg/ml), with a specificity of 89% and sensitivity of 42% (60) → left atrial stiffness

Clinical manifestations and organ involvement

- It is still debated whether SSc is specifcally associated with an increased prevalence/incidence of coronary artery disease.
- **a recent study:**
- epicardial adipose tissue (EAT) thickness was significantly greater in patients with SSc compared to healthy controls and correlated positively with age, erythrocyte sedimentation rate (ESR), CRP, insulin,haemoglobin A1c and total and LDL cholesterol
- In cohort study:

patients with SSc had :

- more established cardiovascular risk factors
- increased relative risk of developing cardiovascular diseases(such as myocardial infarction, peripheral vascular disease, aortic and mitral regurgitation) at the time of diagnosis and during follow-up

Clinical manifestations and organ involvement

- In the last few years there has been increasing interest in cardiac MRI as a technique to diagnose heart oedema and/or fibrosis

- Recent study confrmed the role of cardiac MRI in the evaluation of SSc patients detecting :
  - myocardial inflammation on cardiac MRI in 73%
  - increased risk of myocardial inflammation was associated with young age and high mRSS at onset
  - Neither the SSc subset, internal organ involvement, inflammatory markers, nor cardiac and muscle enzymes were associated with myocardial inflammation in SSc

Clinical manifestations and organ involvement

- after a follow-up of 43 months (multivariate analysis); **myocardial fbrosis seems to represent a predictor of cardiovascular outcomes in SSc.**
- association between CRP and mortality
- myocardial fibrosis in middle LV segments and older age were predictors of heart failure
- higher maximum mRSS as it seemed to be associated to coronary artery disease.
- although further studies will be necessary to better understand the association of mRSS and heart disease

Clinical manifestations and organ involvement

- high sensitive biomarkers for heart involvement and mortality in SSc: cardiac troponin T (hs-cTnT)and NT-proBNP levels

- patients positive for both markers :
  - lower left ventricular ejection fraction (LVEF)
  - higher rate of right bundle branch block (RBBB)

- Autonomic dysfunction was identifed as an early marker of SSc progression and could precede cardiac fbrosis occurrence

Clinical manifestations and organ involvement

- a reduced vagal and increased sympathetic modulation at rest and a blunted autonomic response to orthostatism compared to healthy subjects. Autonomic impairment was mostly detectable in the advanced and fbrotic subset of SSc and it is not an early maker of dysfunction in this population

- **An Iranian study reported:**

that BBBs and the fragmented QRS complex were more prevalent in SSc patients (27% and 37%, respectively), without any association with the involvement of the other organs

Clinical manifestations and organ involvement

- **A recent study suggested :**
- a more severe cardiopulmonary manifestation in SSc men than in women, with men in particular presenting a higher incidence rate of RV dysfunction and ILD compared to women, even in the early phase of the disease

- Male sex, low % DLCO, exercise oxygen desaturation, anaemia, abnormal dyspnea scores and baseline pericardial effusion were strongly associated with higher mortality

- Risks for cardiopulmonary hospitalisation were associated with increased dyspnoea and pericardial effusions, although PH patients with DLCO <50% had the highest risk of cardiopulmonary hospitalisations

Clinical manifestations and organ involvement

Renal involvement

- A retrospective study analysed the demographic, clinical and laboratory data of SSc patients who developed SRC after the disease compared to control subjects (SSc without SRC events)
- not show a significant difference in the proportion of black race in SSc with SRC compared to controls
- two groups showed clinical differences in the frequency of PH and cardiac involvement in SRC group
- a higher rate of anti-Ro and anti-RNA polymerase III antibodies and control subjects were characterised by anticentromere and antinuclear antibody positivity

Clinical manifestations and organ involvement

- presence of three or more of the following laboratory alterations :

proteinuria, chronic kidney disease, elevated erythrocyte sedimentation rate,thrombocytopenia, anaemia, anti-Ro and anti-RNA polymerase III antibodies) and clinical manifestations (hypertension)

associated to SRC development (sensitivity 77% and specifcity 97%)

- Kidney involvement may be subclinical or it may occur with several clinical manifestation:

- mild proteinuria
- reduction of estimated glomerular filtration rate
- high renal resistive indices(RRI:peak systolic velocity/end diastolic velocity)

Clinical manifestations and organ involvement

- Positive correlation of RRI with age and sPAP, and a negative correlation with creatinine clearance and DLCO

- high RRI:
  - associated with diffuse skin fbrosis, history and/or presence of digital ulcers, sPAP, presence of lung involvement with a correlation both with ILD on chest HRCT and lower FVC and DLCO by univariate correlation.
  - association with death, cardiac and renal worsening

  - **importance of RRI in the evaluation of SSc patients from the early phases of the disease**

Clinical manifestations and organ involvement

- Gigante *et al*. recently subjected 92 SSc patients and 40 healthy subjects to renal ultrasound (US), evaluating renal morphological variables:

  - A signifcant higher renal length, parenchymal thickness and renal sinus was reported in healthy controls compared to SSc subjects.
  - RRI was higher in SSc patients
  - glomerular fltration rate was signifcant lower in SSc patients

possible presence of a subclinical renal involvement indicating renal and Doppler US as a fundamental screening examination to perform in SSc

Clinical manifestations and organ involvement

Gastrointestinal involvement

- reflux and diarrhoea, more common
- (GERD) symptoms : affect the quality of sleep and increase in fatigue with a deductible impact on quality life And depression
- correlation between the risk of malnutrition, skin involvement, depressive symptoms and ILD
- GI involvement may be present from the early phase of the disease and in asymptomatic patients who may present an abnormal oesophageal manometry

Clinical manifestations and organ involvement

- **all patients presented an alteration of at least one of the three phases of swallowing (oral, pharyngeal, oesophageal)revealed by VFG:**
- oral phase was the less frequently affect
- pharyngeal phase presented alterations in a higher proportion of subjects.
- oesophageal phase was frequent ,particular an abnormal motility of the upper oesophageal sphincter (UES) (12.7%)and lower oesophageal sphincter (LES)(76.4%),
- inadequate primary peristalsis(52.7%),abnormal secondary peristalsis (29.1%) and non-peristaltic contractions (40%)
- patients with lcSSc and dcSSc presented some signifcant differences in the oesophageal phase as an inadequate primary peristalsis, and a defcit of oesophageal clearance seemed to be morefrequent in dcSSc.

Clinical manifestations and organ involvement

- hernia was signifcantly more frequent in lcSSc.

- **In one study: 79 patients with or without gastroesophageal symptoms underwent upper GI endoscopy:**
- higher frequency of hiatal hernia in symptomatic patients

- similar frequency of the other endoscopic and histopathological fndings (gastric polyps, oesophageal ulcers, HP positivity, endoscopic gastritis) among symptomatic and asymptomatic subjects.

- Barrett's oesophagus in 5 patients
  watermelon stomach was revealed in 2 patients

Clinical manifestations and organ involvement

- **Adarsh *et al*. confrmed :**
- oesophagitis (19 patients/21, 83%) by (EGDS) in SSc patients.
- The most common duodenal abnormalities included an excess of mononuclear inflammatory cells in lamina propria and a partial villous atrophy

- **Kuribayashi *et al*. evaluated oesophageal involvement in more than 100 SSc patients by EGDs and manometry:**
- relationship between oesophageal motility alterations and skin involvement.

- **possible double aetiology of ILD: both due to the disease activity itself and to gastroesophageal reflux events.**

Treatment

- ***Vasoactive treatment***
  Vascular alterations play a key role in SSc pathogenesis of PAH, RP, DUs and renal crisis

- the DeSScipher study :

  33.8% of patients with previous or current DU were treated with CCBs alone

- PROSIT study:

- ✓ iloprost, a synthetic analogue of prostacyclin PGI2, is the frst-line choice for the management of severe RP and DUs, when oral therapy fails
- ✓ It represents an effective and quite well tolerated option,.

Treatment

- **An Expert Consensus based on a systematic literature review suggests :**
- ✓ a 1–3-day monthly regimen for RP and DU healing, while 1 day monthly for DU prevention.

- **Riociguat** is an elective soluble guanylate cyclase stimulator, currently approved for treatment of PAH and PH due to chronic thromboembolism

- **A multicentre randomised, double-blind, placebocontrolled pilot study evaluated the effect of riociguat on DU burden:**
- ✓ no evidence of effcacy during the 16-week FU period

- ✓ Nevertheless, during the open-label extension,the patients treated saw the complete healing of their DUs, suggesting that a longer duration of therapy is needed to obtain results.

Treatment

- **An observational study aimed to assess the role of bosentan in functional impairment, RP and DU-related symptoms:**
- ✓ improvement in HAQ-DI, VAS-R and VAS-DU scores in response to bosentan therapy over the 1-year follow-up period
- ✓ 2 of the 41 patients had to stop treatment due to elevated liver enzymes,with rapid normalisation after suspension of the therapy.
- ✓ PAH-related symptomsnhave a high functional impact and are diffcult to treat

- **a randomised, controlled, double-blind, parallel group study:**
- ✓ investigated the effcacy of early use of ambrisentan in patients with mildly elevated mPAP did not signifcantly differ in treated patients and the control group
- ✓ signifcant improvements in the cardiac index and pulmonary vascular resistance (PVR) at rest and during exercise

Treatment

- ***Antifbrotic treatment***

Nintedanib :

- ✓ small molecule tyrosine kinase inhibitor acting on the PDGF, VGF and VEGF receptors and thus target cytokine-induced activation of fibroblasts

- ✓ Recently, nintedanib, approved for idiopathic lung fbrosis, is being investigated also in ILD related to scleroderma with favourable results

Treatment

- **An *in vitro* study :**
- nintedanib to reduce lung fbroblast proliferation and migration
- reduce extra-cellular matrix (ECM) molecule expression and the transition of LF to activated and contractile myofbroblasts which are correlated to the progression of the fbrotic process.

In the present study the *in vitro* exposition amount of drug needed to reach the outcome is consistent with the *in vivo* therapeutic range of nintedanib, suggesting that this drug could have a stronger antifbrotic effect for scleroderma patients.

Treatment

- 576 patients with SSc related ILD were 1:1 randomised to receive 150 mg bid nintedanib or placebo. In both groups, patients with diffuse and limited cutaneous SSc were equally represented, and about half of the entire population was taking MMF.The outcomes were evaluated after 52 weeks, evidencing :

- ✓ a lower rate of decline in FVC in the nintedanib group
- ✓ Differences between groups were fewer than expected also because FVC in the placebo groups showed a minor decrease with respect to the one observed in the placebo group of the study performed in IPF
- ✓ presence of patients with limited cutaneous SSc, as well as the use of MMF, may constitute bias in SENSCIS. The study did not demonstrate any effcacy of this molecule in other scleroderma-relatedfbrosis such as skin

Treatment

WNT Signalling as a Target in SSc

- ✓ Wnt is a highly conserved signalling pathway that is involved in organ development ,cancer and fibrosis

- ✓ Enhanced Wnt signalling has been found in SSc with higher levels of the Wnt agonists both in the blood and tissues from patients
- ✓ A recent clinical trial in SSc patients using C-82(active metabolite of PRI-724) to block Wnt signalling :
- ✓ well tolerated and reduction in a specific cluster of genes known to be associated with SSc

however, no clear clinical benefit was shown but it could the treatment regime needed longer to reverse long-standing fibrosis.

Treatment

The Endocannabinoid System

- **There are three classes of cannabinoids:**
- endogenous cannabinoids
- phytocannabinoids
- synthetic cannabinoid

- **two types of cannabinoid receptors: CB1 and CB2**
- **It has been shown that both CB1 and CB2 are upregulated in SSc dermal fibroblasts in culture**

Treatment

- **synthetic cannabinoid:**
- reduced collagen 1 production.
- downregulation of TGF-β1 ,Interleukin-6
- abrogated dermal fibrosis in the bleomycin model of fibrosis

- **It appears that the CB2 receptor is important for the therapeutic anti-fibrotic effects of cannabinoid agonists in SSc**

lenabasum, recently revealed in a phase II study .The phase 3 trial is now underway with enrolment complete.

Treatment

Serotonin/5HT

- ✓ Serotonin is a neurotransmitter
- ✓ in SSc patients, serotonin is released and binds to fibroblasts to induce tissue fibrosis (mediated through the 5-HT2b receptor)
- ✓ This receptor is hugely overexpressed in SSc skin and hepatic stellate cell
- ✓ 5-HT2b-specific receptor blocker terguride and cyproheptadine-reduced fibrosis in animal model
- ✓ Terguride is already licenced for use. A phase III trial is now underway

Treatment

targeting of Nuclear Receptors

- ✓ Nuclear receptors are a family of transcription factors that appear critical in fibrosis

- ✓ PPAR-γ is a key nuclear receptor that is activated by fatty acids that are downregulated in SSc cells and tissues and .PPAR-γ agonist rosiglitazone reduces fibrosis in animal models of SSc

Rosiglitazone is already licenced.

- ❖ **Recently, a pan PPAR agonist molecule :**
- ✓ developed and was found to be potently anti-fibrotic in multiple animal models of fibrosis
- ✓ effective in lung fibrosis and pulmonary hypertension in the Fra2 mouse model

Treatment

Immunosuppressive treatment

- **A descriptive, retrospective cohort claims analysis made in a healthcare insurance database found :**
- ✓ 30.8% of 7812 patients received immunosuppressants (IMT) during the frst year after SSc diagnosis
- ✓ 43.8% hydroxychloroquine and 21.1% methotrexate and 46.5% were treated with corticosteroids (CS)

Treatment

- there are no controlled clinical studies evaluating the effcacy of CS as a monotherapy in SSc,whereas improvement or stabilisation of lung function and skin involvement in combined therapy

- the safety of CS is controversial, and sometimes associated with an increased mortality and morbidity risk due to their side effects (95).

Treatment

- **An ongoing double blind RCT is investigating the effect of high dosage of methylprednisolone in thirty patients with very early SSc.:**
  - CS have the power to effciently stop inflammation and arrest disease progression

- **An experimental study on 21 SS patients evaluated *in vitro* effects of dexamethasone on cytokine production in peripheral blood mononuclear cells (PBMC):**
  - IL-2, which did not change signifcantly.

Treatment

- **cyclophosphamide (CYC):**

some retrospective studies enhance CYC effectiveness in reduce skin thickening , its main application remains in ILD treatment

Efforts are being made to fnd alternative drugs, available data show that the duration of its benefts after suspension is short and it accounts for many and severe sides effects.

Treatment

- mycophenolate mophetil

- MMF is being considered as an alternative to CYC.
- **In the SLS II study:**
  the two treatments produced similar improvements in FVC% predicted at24 months, with better tolerability and safety given by MMF
- DLCO %-predicted and DL/VA %-predicted decreased less during treatment in the MMF arm than in the CYC arm
- **Volkmann *et al*:**
- (105) dosed CCL-18 and KL-6 – two pneumoproteins considered as predictors of ILD progression – at baseline and after 24 months in the two SLS II arms:
- their level in patients assigned to MMF experienced the greatest decline.

Treatment

- **volumetric HRCT scans were performed at baseline and at the 2-year follow-up in the two groups and transitional radiographic changes in patterns of ILD have been analysed by Kim *et al*:**

- The authors calculated the differences in the probabilities of changes from one ILD pattern to another by using voxel-by-voxel transitional scores on paired HRCT scans :
- lung fbrosis, ground glass (GG), honeycombing

no difference between the two treatment arms, thus indicating a comparable effcacy of CYC and MMF in improving radiological evident lung damage

Treatment

- **Intravenous immunoglobulins (IVIg)**

  used in skin fbrosis, ILD, GI involvement in ssc

- A recent retrospective study on 52 patients with SSc-associated myopathy was conducted. Having a signifcantly higher maximal CS dose at baseline, IVIg-treated patients showed:

✓ a greater decrease of CS at 3 months

✓ a lower CS dose at one year

✓ at the end of follow-up so that, in presence of an acceptable tolerance profle

this study supports the use of IVIg as a CS-sparing agent

Treatment

Targeting B Cells

- SSc is associated with specific auto-antibodies → B cells are intimately involved

- Rituximab:
  - ✓ monoclonal antibody to CD20 and its mechanism of action is thought to be depletion of B cells
  - ✓ reduction in skin score and also prevention of worsening of FVC?

- Further studies are warranted into the effects of rituximab, if there is any benefit in using with background MMF.

Treatment

- **Rituximab (RTX) was compared to CYC in an open RCT evaluating both skin and lung outcomes:**
- The study enrolled 60 patients with skin and lung involvement, randomly receiving monthly pulses of CYC 500 mg/m2 orRTX 1000 mg at baseline and after 15days. At 6 months:
- FVC in the RTX group signifcantly improved, while it declined in the CYC
- mRSS improved signifcantly more in the RTX group
- major adverse events observed only in patients receiving CYC

- **longitudinal cohort by Elhai *et al*:**
- did not highlight signifcant improvements on lung fbrosis in patients treated with RTX.

Treatment

Targeting of Interleukin-6

- IL-6 is a classic pro-inflammatory cytokine that is also potently pro-fibrotic

- The levels of IL-6 are higher in SSc blood and also in the tissues.

- increase in collagen and other ECM is due to downstream STAT3 signalling suggesting that IL-6 is a therapeutic target in the diseas

- Based on these in vitro findings, animal models and a few case reports tocilizumab:

✓ no significant improvement in the change from baseline to week 48 modified Rodnan skin score (mRss)

✓ clinically meaningful changes in lung function (less decline in FVC)

✓ **unlikely that this will now be licenced for SSc**

Treatment

- **Results from a multicentric, double-blind, randomised, placebo-controlled study (the faSScinate study) involving TCZ evidenced:**
- decrease in mRSS although signifcant between-group differences were not observed
- signifcant leser reduction in FVC was also evident in the treated group at week 24 but it was not maintained at week 48.
- while TCZ therapy did induce a trend of effcacy similar to the one of the phase 2 trial, there is potential retardation of the progression of lung fbrosis in these patients

Treatment

- a randomised parallel group study was conducted comparing 6 patients maintained on conventional therapy with 7 patients who received an additional 8mg/kg/ month infusion of TCZ(6 months):
- non-signifcant reduction of mRSS in the TCZ-receiving patients
- in patients with short disease duration,high CRP, low IL-13 and low CCL5,a possible SSc endotype responsive to TCZ therapy

Treatment

Interleukin-13

- IL-13 is a cytokine that was found to promote IgE class switching and inhibit pro-inflammatory cytokines.

- T cells in SSc produce high levels of IL-13 → pro-fibrotic

- SAR156597 is a monoclonal antibody targeting IL-4 and IL-13 :

✓ phase II proof of concept placebo-controlled trial is now ongoing in SSc

✓ phase II trial has been undertaken in idiopathic pulmonary fibrosis, which did not have positive results

Treatment

Interleukin-31

- IL-31 synthesised by activated Th2 cells
- IL-31:
  - ✓ associated with pruritus
  - ✓ high levels of IL-31 in SSc serum and that this is directly profibrotic
  - ✓ mediated through phosphorylation of STAT3 and its receptor is regulated epigenetically in SSc

- Nemolizumab is a monoclonal antibody that targets the IL-31 receptor and has been shown to be helpful and relieve the itch in atopic dermatitis

Treatment

Abatacept

- T cells play a prominent role in early disease in ssc

- Abatacept:
  - ✓ fusion protein of the Fc region of IgG1 and the extracellular domain of cytotoxic T lymphocyte– associated antigen 4 (CTLA-4)
  - ✓ blocks the interaction of CD28 on the T cell and CD80/86 on the dendritic cell
  - ✓ approved for RA
  - ✓ a phase II trial was undertaken in early diffuse SSc patients; abatacept was well tolerated but that the change in mRss was not significant

Treatment

Interferon

- Anifrolumab:
- ✓ antibody against the type I interferon receptor
- ✓ In a phase I multicentre, open-label study in SSc patients, to be safe and tolerable but not efficacy was assessed

Bardaloxone Methyl:

- ✓ currently being tested in a clinical trial for SSc associated pulmonary hypertension
- ✓ nrf-2 stimulator, which should reduce oxidative stress and fibrosis.

Treatment

Abituzumab

- humanised IgG2 antibody targeting γv subunit (CD50) integrins

- Integrins :
  - activate TGF-β. a key pro-fibrotic molecule
  - integrin avβ5 is upregulated on SSc dermal fibroblasts and upregulation of this integrin leads to enhanced deposition of collagen

- A phase II trial of abituzumab is currently recruiting about 180 patients with SSc and interstitial lung disease with and FVC 40–85% predicted : primary endpoint is the change in baseline in absolute FVC at week 52.

Treatment

Janus Kinase Inhibition

- Janus kinases (JAKs) are non-receptor tyrosine kinases.They transduce cytokine signals via phosphorylation of STATs

- Tofacitinib :
- JAK1 and JAK3 inhibitor
- licenced for rheumatoid arthritis
- Tofacitinib is currently undergoing clinical trials in diffuse SSc in a phase I/II randomized trial. In a recent abstract, there was a trend towards improvement in the mRss

- Selective JAK2 inhibitors :
- reduced collagen in SSc fibroblasts and in vivo in multiple animal models

Treatment

- ***Cell transplantation***
  - **(auto-HSCT)**

✓ is shown to be effective in severe and rapidly progressive form of the disease, regarding cutaneous and pulmonary involvement

❖ **A *post-hoc* analysis on a phase I/II clinical trial conducted on 19 patients with severe SSc was performed to evaluate whether the transplantation of CD34-selected cells (11 patients) instead of unmanipulated HSCs (8 patients):**

✓ more effective in improving disease activity in CD 34 selected cell

✓ The group treated with CD-34 selected cells experienced a higher beneft in mRSS and in FVC and its duration was longer

Treatment

- **Assassi *et al*:analysis of the global molecular changes at the whole blood transcript and serum protein levels of 62 participants (27 HSCT and 35 CYC) of the SCOT study, as well as of 62 matched unaffected controls:**
- ✓ individuals with SSc, compared to controls, have a marked IFN, neutrophil, and inverse cytotoxic/NK cell transcript signatures which were corrected by HSCT but notby CYC.
- ✓ These changes correlated with improvement in the lung volumes and skin fibrosis

Treatment

- **Autologous adipose stem cell (ADSC):**
  - ✓ surgical intervention proposed in the treatment of SSc-related oro-facial fbrosis
  - evaluated in a cohort of 62 SSc patients :
  - ✓ signifcative improvement in all domains of mouth function assessed by the MHISS score.
    aesthetical and psychological benefts
  - *in vitro* analysis:
    a reduced expression of proinflammatory and profbrotic mediators

Treatment

❑ *Physiotherapic treatment*

- ✓ Physiotherapy, occupational therapy, local treatment and electromedical devices are gaining attention in the management of SSc
- ✓ Self-administered stretching programmes for both face and hands trying to help maintain function.

- ❖ A recent feasibility study was performed to assess the safety, tolerability and beneft in the management of DUs in SSc:
- ✓ tolerability with a reduction in pain and an improvement of the vascularisation measure by laser Doppler perfusion imaging
- ✓ A physical medicine regimen provides benefts also in the management of RP in SSc2

Treatment

- ✓ Carbon dioxide (CO_2) hand immersion has proven its effcacy in increasing distal digital blood flow in patients with peripheral arterial occlusive disease and it has also been considered in primary and secondary Raynaud's syndrome.

- ❖ **Lange *et al* evaluated the effect on acral perfusion of CO_2 enriched hand bath :**
- ▶ ultrasound with measurements of the resistance index (RI) of digital arteries: signifcant reduction of the RI in the CO_2-receiving patients but not in the patients treated with hot water or in the healthy controls.

Conclusion

- SSc is a complex heterogenous disease whose clinical cours is unpredictable.
- Knowledge in this appalling condition, SSC, is rapidly growing.
- Genetics and epigenetics are providing insights into potential targets for innovative therapies and precision medicine.
- Several attempts have been published this last year to try to improve patient stratifcation and risk prediction.
- The prognosis has been clarifed and it is now clear that the heart and lungs are the leading causes of disease-associated deaths

Conclusion

- If major organ involvement is still a concern, for a large proportion of patients, quality of life impairment and disability are the primary consequences of the disease
- nintedanib has been approved for a lung disease associated with SSc, but this does not modify the skin fibrosis.
- Many new targets are emerging, and this review has highlighted some of these. It may well be that target identification of the molecular pathway prior to entering the clinical trial for a designated target helps enrich.