Poster Tours – *Clinical*

Poster Tour 1: *Raynaud & Ulcers*

PS01

DECREASE OF BRACHIAL ARTERY ENDOTHELIAL-DEPENDENT FLOW-MEDIATED DILATION CHARACTERIZES VERY EARLY SYSTEMIC SCLEROSIS (VEDOSS) PATIENTS

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Background. Endothelial dysfunction is a key feature of systemic sclerosis (SSc) preceding and potentially contributing via tissue ischemia to the widespread fibrosis characteristic of this condition. Multiple studies have revealed an increased prevalence of large-vessel disease in patients with SSc. Recently new preliminary criteria for very early diagnosis of systemic sclerosis (VEDOSS) have been proposed. The aim of this study was to investigate the endothelial dysfunction through brachial artery endothelial-dependent flow-mediated dilation (FMD) in patients with Raynaud's phenomenon (RP).
Methods. 42 consecutive patients with RP were enrolled. Patients were divided into 3 study cohorts: patients with primary RP with normal capillaroscopic findings and without any autoantibodies (n=10), VEDOSS patients (n=8) and defined SSc patients(n=24), respectively. Ten gender and age matched healthy individuals were enrolled as control group. Demographic, clinical and immunological parameters have been collected at the beginning of the study. 11 out of 24 (45.8%) SSc patients presented history of ulcers. Ultrasound assessment of FMD was performed in all RP subjects and in healthy subjects to evaluate endothelial dysfunction. VEGF, VEGF-RII, IL-6 and IL-6R plasma were determined through ELISA.
Results. FMD was significantly reduced in patients with SSc compared to healthy subjects and compared with primary RP patients(SSc:6.9±6.3% vs HS:18.6±7.0% and RP:10.2±5.2%; $p<0.0001$ and $p=0.024$ respectively). The impairment of FMD was comparable in VEDOSS patients and in SSc patients, but interestingly also the VEDOSS patients presented a significant reduction of FMD when compared with healthy controls and primary RP controls (VEDOSS:5.1±3.6% vs HS:18.6±7.0% and RP:10.2±5.2%; $p<0.0001$ and $p=0.04$ respectively]. IL6 levels were significantly higher in patients with SSC compared to healthy controls, primary RP and VEDOSS patients (SSC:3.8±4.6% vs HS:2.0±3.0%, RP: 0.9±0.4% and VEDOSS:1.8±1.3%; $p=0.03$, $p<0.0001$ and $p=0.02$ respectively). VEGF plasma level was increased in SSc patients compared to healthy controls (SSC:26.6±38pg/ml vs HS:13.8±25.9pg/ml; $p=0.05$). Considering the clinical features of SSc patients no differences in cytokines levels and in FMD emerged. IL6 plasma levels directly correlate with skin score value in SSc patients (R=0.41; $p=0.03$).
Conclusions. An impairment of FMD was present in patients with RP, in particular in SSc and VEDOSS patients, suggesting a contemporary impairment of microvascular and macrovascular compartments in these patients. The deeper FMD impairment that characterized either SSc and VEDOSS patients, suggests that the endothelial dysfunction is already established since the early phases of the disease. However, the increased circulating levels of IL6 found in SSc patients, suggests its possible inflammatory action on endothelial dysfuction inducing SSc organ damage.

PS02

DIAGNOSTIC STANDARDS FOR CHILDREN WITH RAYNAUD'S PHENOMENON

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Background. Raynaud's phenomenon (RP) can be the first symptom of a connective tissue disease in children, in particular juvenile systemic scleroderma (JSSC) or systemic lupus erythematosis (SLE). However, the prevalence of RP in healthy school children has been shown to be as high as 15% (1). There are currently no guidelines or agreed management strategies amongst Paediatric Rheumatologists on how to differentiate primary from secondary RP or how often patients require evaluation.
Objectives. To develop consensus standards for good clinical practice for children with RP.
Methods. A consensus meeting was organized in the frame of the PRES scleroderma working group. A nominal group technique was used. 75% consensus was defined as agreement.
Results. The following agreements were reached:
1. All patients with RP should be screened with an ANA test.
2. All ANA positive patients should be screened for scleroderma-specific antibodies (*e.g.* anti-SCL 70 and anti- centromere antibodies).
3. All patients with RP should be investigated by capillaroscopy. Capillaroscopy will be classified into 'normal', 'aspecific changes' or 'scleroderma pattern'.
4. All patients who have additional symptoms pointing to a definite connective tissue disease should be evaluated according to disease specific guidelines.
5. ANA-negative and capillaroscopy-negative patients should be followed-up at least every 6 months.
6. ANA positive patients without disease-specific antibodies and with negative capillaroscopy findings should be followed-up at least every 6 months.
7. ANA and disease-specific antibody positive patients should have organ specific evaluation according to symptoms, examination and relevant to that particular disease *e.g.* patients who are ANA and Scl-70 positive may need organ specific evaluation for JSSC as per the Juvenile systemic sclerosis inception cohort protocol (www.juvenile- scleroderma.com).
8. ANA-positive patients, who have no disease specific antibody but have positive capillaroscopy results, should be followed-up at least every 3 months.
9. ANA-negative patients with positive capillaroscopy result should be followed-up at least every 6 months.
10. The group could not reach an agreement regarding treatment, due to a lack of data for the paediatric age group. The group agreed that implementation of adult recommendations for paediatric care might be reasonable, but robust paediatric trials are needed.
Conclusions. The group made a suggestion for a standard of good clinical practice for RP in children. Our aim is that this will facilitate a large multicentre prospective follow-up study of children with RP.
References
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PS03

ANTI-ENDOTHELIAL CELL ANTIBODIES AS BIOMARKER OF SEVERE VASCULAR MANIFESTATIONS IN SYSTEMIC SCLEROSIS

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Background. Systemic sclerosis (SSc) is a connective tissue disease of unknown etiology characterized by vasculopathy. Vascular injury occurs early in the course of disease, and previous studies suggest a primary role of anti-endothelial cell antibodies (AECA). The aim of the present study was to assess the association between AECA and the occurrence of severe vascular events in SSc patients.
Methods. Fifty-eight SSc patients with severe vascular manifestations (19 with digital ulcers and amputation, 36 with symptomatic pulmonary arterial hypertension and 3 with scleroderma renal crisis), 62 SSc patients without severe vascular manifestations (20 with diffuse cutaneous SSc, 22 with limited cutaneous SSc and 20 with SSc sine scleroderma) and 60 healthy controls were included in this study. Sera were examined for the presence of IgG-AECA, using a cellular enzyme-linked immunosorbent assay (Cyto-ELISA). Human umbilical vein endothelial cells (HUVEC) were used as antigenic substrate for Cyto-ELISA.
Results. Serum IgG-AECA levels in SSc patients with severe vascular manifestations (p=0.0001) as well as in those without these manifestations (p=0.038) were significantly higher than in the control group. Subgroup analysis showed that only patients with digital ulcers and amputation (p=0.001) and those with symptomatic pulmonary arterial hypertension (p=0.019) had significantly higher levels of AECA compared to controls. The frequency of IgG-AECA was significantly higher (29%) in patients with major vascular events (47% in patients with digital ulcers and amputation, 22% in patients with symptomatic pulmonary arterial hypertension and 0% in patients with scleroderma renal crisis) than in patients without these events (13%) (20% in patients with diffuse cutaneous SSc, 14% in patients with limited cutaneous SSc and 5% in patients with SSc sine scleroderma) (p=0.041). Thirty-eight percent of patients with digital ulcers had these antibodies, versus 6% of those without digital ulcers (p=0.022).
Conclusion. The strong association of IgG-AECA with major vascular events introduces these antibodies as an important serological biomarker for vascular disease severity in systemic sclerosis.

PS04

NAILFOLD VIDEOCAPILLAROSCOPY AND OTHER PREDICTIVE FACTORS ASSOCIATED WITH NEW DIGITAL ULCERS IN SYSTEMIC SCLEROSIS: RESULTS FROM THE CAP STUDY

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Background. Digital ulcers (DU) are painful, disabling and affect almost 50% of systemic sclerosis (SSc) patients. Nailfold videocapillaroscopy (NVC) non-invasively assesses SSc-related micro-angiopathy and may be useful in predicting DU (1–4).
Objective. To identify NVC variables and other factors which predict the occurrence of new DU in SSc patients.
Methods. International, prospective, cohort study in SSc patients, with two strata: DU-history and No-DU-history at enrollment. The No-DU-history patients had to be diagnosed within the last two years. Eligibility was not restricted by medication use. Baseline clinical characteristics including locally evaluated, standardized NVC (fingers II-V) were collected. Patients were followed up to 6 months for new DU. Univariable and Multivariable Logistic Regression (ULR and MLR) was performed to assess statistical significance (Wald Chi-square) of variables and their discriminatory ability (receiver operating characteristic area under the curve (ROC AUC). Internal model validation was performed by bootstrap method.
Results. Of the 623 patients enrolled (14 countries, 59 centers), 591 had data on DU-outcome [new DU (Cases) or no new DU (Non-cases)]. 468 (79%) patients had a DU history, of whom 103 (22%) developed new DU. 123 (21%) patients had no DU history, of whom 5 (4%) developed new DU. The present analysis focuses on the DU-history stratum (mean age 54.0 years, 79.5% females, 59.8% with limited cutaneous SSc).
Three baseline variables were selected in the final prognostic model: i) Mean number of capillaries/millimeter (middle finger, dominant hand) of 3.8 (95%CL 3.5, 4.2) in Cases and 4.7 (4.5, 4.9) in Non-cases (Wald p<0.001; ROC AUC=0.614 [95%CL 0.553, 0.674]); ii) Mean number of DU 1.8 (95%CL 1.2, 2.4) in Cases and 0.6 (0.4, 0.7) in Non-cases (Wald p<0.001, ROC AUC=0.678 [95%CL 0.622, 0.734]); iii) Critical digital ischemia present in 14.6% of Cases and in 3.3% of Non-cases (Wald p<0.001; ROC AUC=0.556 [95%CL 0.521, 0.592]); The prognostic model had a ROC AUC of 0.738 (95%CL 0.681, 0.795). Bootstrap results were consistent with the final model.
Conclusions. NVC imaging and assessment are feasible in international multicenter studies. The model for DU prediction in SSc patients with a history of DU uses number of capillaries (middle finger, dominant hand), current number of DU, and current critical digital ischemia. The model may add to the available tools for the early detection of SSc patients at high risk of developing new DU.
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PS05

MICRORNA-34A AND MICRORNA-155 IN RAYNAUD PHENOMENON: POSSIBLE EPIGENETIC BIOMARKERS OF ENDOTHELIAL DYSFUNCTION IN SYSTEMIC SCLEROSIS.

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Aim of the study. MicroRNAs(miRs) are a novel class of post-transcriptional regulators implicated in the pathogenesis of distinct human pathologies. MiR-34a and miR-155 were found to be related to endothelial senescence and inflammation. The aim of this study was to investigate the expression of miR-34a and miR-155 in peripheral blood mononuclear cells(PBMCs) in Systemic sclerosis(SSc).
Methods. Twenty-seven consecutive patients with Raynaud phenomenon(RP) were enrolled in this exploratory study. Patients were divided into 3 study cohorts: patients with primary RP (n=8), early SSc patients(eSSc) (n=9) fulfilling the proposed Very Early Diagnosis Of Systemic Sclerosis (VEDOSS) criteria and definite SSc patients (n=10) respectively. Gender and age matched healthy individuals (n=7) were enrolled as a control group. Demographic, clinical and immunological parameters have been collected at the beginning of the study. Expression of miR-34a and miR-155 was evaluated by qPCR on PBMCs. To identify miR-34a HumanTargetScan cross-referenced was employed. Identified targets were verified by qPCR. VEGF, VEGF-RII, IL-6 and IL-6R plasma levels were determined through ELISA.
Results. MiR-155 is overexpressed either in PBMCs of SSc (p=0.04) and eSSc (p=0.0002) compared to healthy controls. MiR-34a expression is increased only in SSc compared to healthy controls (p=0.013). Patients with primary RP did not differ for miR-155 and miR-34a expression from healthy controls (p>0.05). Anti-Scl70+SSc patients have significantly higher expression of miR-34a in PBMCs compared to anti-centromere+SSc patients (p=0.04). Furthermore, SSc patients with active and/or previous digital ulcers have significantly higher miR-34a expression compared to patients without ulcers (p=0.01). Finally the expression of miR-34a directly correlated with skin score value (R=0.52, p=0.032) in both SSc and eSSc patients and with IL-6 plasma levels (R=0.42, p=0.01). IL-6 receptor (IL6-R) was selected as target of miR-34a. IL6-R gene expression was significantly higher in eSSc patients compared to SSc (p=0.02). VEGF plasma levels were significantly higher in SSc patients compared to healthy control(p=0.01) as well as IL-6 plasma levels (p=0.02).
Conclusions. The increased expression of miR-34a and miR-155 in PBMCs differentiates SSc patients from RP patients. The overexpression of miR-155 was already found in eSSc, suggesting a possible endothelium impairment since the early phases of the disease. The increased expression of miR-34a in PBMCs of SSc patients, together with the down regulation of its target gene, IL6-R, characterize the subsequent vascular impairment and specific organ involvement associated to increased IL-6 circulating levels. Therefore miRNAs expression analysis could be an useful tool to differentiate between primary and SSc associated RP.

PS06

PHOSPHODIESTERASE-5 INHIBITORS FOR THE TREATMENT OF SECONDARY RAYNAUD'S PHENOMENON: SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED TRIALS

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Introduction. Recent controlled trials have assessed the efficacy of phosphodiesterase-5 (PDE-5) inhibitors in secondary Raynaud's Phenomenon (RP). However, the conclusions are conflicting and whether these drugs are effective remains unclear. The objective of this systematic review and meta-analysis was to determine the efficacy of PDE-5 inhibitors on the Raynaud's Condition score (RCS), the frequency and the duration of attacks.
Methods. A systematic review of articles was performed (sources included Medline, Embase, Web of Science, the Cochrane Central Register of Controlled Trials). Only double-blind, randomized, controlled trials (RCTs) were included. Study selection was done independently by 2 authors using predefined data fields, including study quality indicators. The PRISMA statement guidelines were followed.
Results. Six RCTs were included (1 with sildenafil, 1 with modified-release sildenafil, 3 with tadalafil and 1 with vardenafil). PDE-5 inhibitors significantly decrease mean RCS by -0.46 [-0.74;-0.17] (p=0.002), the daily frequency of ischaemic attacks by -0.49 [-0.71;-0.28] (p<0.0001), and daily duration of RP attacks by -14.62 [-20.25;-9] min (p<0.0001).
Conclusion. This meta-analysis shows that PDE-5 inhibitors significantly improve RCS, frequency and duration of RP attacks as compared with placebo in secondary RP. However, this effect is moderate and seems to be comparable to that of CCBs.

Poster Tour 2: *Raynaud & Ulcers*

PS07

CHARACTERIZATION OF LOWER LIMB CUTANEOUS ULCERS IN SYSTEMIC SCLEROSIS: THE ANALYSIS OF 554 LESIONS

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Cutaneous ulcers represent one of the most frequent complications in course of systemic sclerosis (SSc). The upper limb ulcers have been evaluated and characterized extensively, but there are only few studies on the lower limb ulcers.
Aim. The aim of the study was to assess prevalence, features and pathogenesis of the lower limb ulcers in course of SSc.
Materials and Methods. Sixty consecutive SSc patients with lower limb cutaneous lesions were enrolled. All patients performed accurate health examination and evaluation of cutaneous lesions, routine blood tests, videocapillaroscopy and arterial and venous lower limb Color Doppler Ultrasonography. Arteriography was performed in patients with occlusive peripheral arterial disease diagnosed at Ultrasonography.
Results. In the lower limbs, 554 different types of lesions were observed. The mean time to healing was 157.5±192 days (median 90 days): the lesions recurred in 25.5% of cases.
Lesions were classified in hyperkeratosis, ulcers and gangrenes. Three hundred forty one (61.6%) hyperkeratoses, 208 (37.5%) ulcers and 5 (0.9%) gangrenes were observed. Ulcers were subsequently divided in: pure ulcers, ulcers secondary to hyperkeratosis and ulcers secondary to calcinosis. One hundred sixty two (77.8%) pure ulcers, 32 (11.1%) ulcers secondary to hyperkeratosis and 32 (11.1%) of ulcers secondary to calcinosis were observed.
Pure ulcers were divided in pure microvascular ulcers 66 (40.7%), venous 58 (35.8%), macrovascular 10 (6.2%) and mixed ulcers 28 (17.3%). Distribution of arterial, venous and lymphatic pathology is shown in table I. Time to healing of the lower limb ulcers correlated inversely to the frequency of medications (p<0,000), as expected. The presence of infection was associated to a significantly longer time to healing (p<0,003).Time to healing correlated also to duration of Raynaud phenomenon (p<0,04) and to duration of SSc (p<0,000).
Rate of recurrence correlated to Raynaud phenomenon (p<0,000) and disease duration (0,000).
Risk of amputation was associated with presence of critical peripheral arterial disease (p<0.05), with duration of Raynaud phenomenon (p<0.000) and with disease duration (p<0.000).
Conclusions. Our data indicate that lower limb lesions have often a multifactorial pathogenesis in SSc. This is the first study that characterized extensively a large number of lower limb cutaneous lesions in SSc. The comprehension of characteristics and pathogenesis of these lesions is essential for their correct management.

Table I.

Peripheral arterial disease (haemodinamically significant	17 (28.3%)
Critical peripheral arterial disease	6 (10%)
Monckeberg medial sclerosis	4 (0.7%)
Venous insufficiency/Post-phlebitic syndrome	18 (30%)
Lymphoedema	13 (21.7%)

PS08

CLINICAL FEATURES AND CHARACTERISTICS OF PATIENTS WITH DIGITAL ULCERS (DU) IN SYSTEMIC SCLEROSIS (SSC) IN THE CZECH REPUBLIC: DATA FROM THE DUO REGISTRY

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Objectives. The aim was to describe disease characteristics of SSc patients with DU and their treatment in the Czech Republic at the time of enrolment.
Methods. In participating centres all patients with current or a history of SSc/DU who have given written consent in accordance with the Czech regulations are enrolled. Here we report on the demographics and treatment of these patients.
Results. Czech patients (n=81) enrolled in the DUO Registry from April 2008 to March 2013, were mostly female (n, %, 71, 87.7%). The disease of the patients was classified as limited SSc in 56.8%, as diffuse SSc in 28.4% and as overlap SSc/mixed connective tissue disease 13.6%. The proportion of patients with at least one ongoing DU at enrolment was 67.9%. DU associated interventions on fingers that were done in the past included upper limb sympathectomy (21%), debridement (23.5%) and surgical amputation (13.6%). Complications that were experienced in the past were mainly gangrene (29.6%), soft tissue infection requiring systemic antibiotics (19.8%), and rarely osteomyelitis (6.2%). At enrolment in the registry, analgesics and anti-inflammatories were administered to 84% of the patients, whereas prostacyclines only to 16%, and endothelin receptor antagonists (ERA) only to 6.2%. Among the topical treatments used (24.7%), topical antibiotics were the most (17.3%), followed by non-adhering dressing (8.6 %). Dry dressing was applied only in 3.7% and hydrocolloids in 2.5%.
Discussion. Considering disease subsets, in the Czech Republic overlap SSc/mixed CTD were more frequent but diffuse subset occurred much less frequent compared to the whole DUO population, were the diffuse subset was 40% (3). The proportion of patients with at least one ongoing DU was higher than in Germany but lower than in France, UK and Italy. Sympathectomy, debridement, and surgical amputation were performed much more often compared to Germany, France, UK and Italy. When evaluating complications, gangrene was more frequent in Czech patients compared to the four countries. Occurrence of soft tissue infection requiring antibiotics was similar only with the Italian population. Treatment with ERA is comparable only with the UK cohort.
Conclusions. The data from the Czech part of the DUO Registry reflect certain national specificities and approaches to the management of SSc patients. The observed differences in other EU countries in patients and disease characteristics, and in management modalities may be also due to selection biases. These findings draw attention to the need for a more harmonised European approach in establishing better management of SSc/DU patients.

PS09

PREDICTORS OF DIGITAL ULCERS IN PATIENTS WITH SECONDARY RAYNAUD PHENOMENON: CORRELATION BETWEEN CLINICAL AND HEMODYNAMIC FEATURES, CAPILLAROSCOPY, ENDOTHELIUM DYSFUNCTION AND ANGIOGENESIS BIOMARKERS.

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Background/Purpose. Digital Ulcers (DU) are a major disabling complication of Systemic Sclerosis (SSc) interfering with personal and professional life of our patients. The aim of our study was to analyze functional dysfunction of endothelium, capillaroscopy and angiogenesis biomarkers inpatients with SSc, with or without peripheral microvascular complications, in order to try to predict the development of digital ulcers in these patients.
Methods. This is a prospective study of a cohort of patients attending our Raynaud´sClinic (n108). Demographic and epidemiological data, autoimmuneserological screening, inflammatory protein screening, Flow mediated dilation(FMD) and end diastolic volume (EDV), capillaroscopy, Endothelin-1(ET-1), ADMA, VEGF andEndoglin were analyzed and compared to a control group (n31). Statistical calculations were performed using SPSS (v 20.0). Comparison and distribution between groups were performedusing Kruskal-Wallis test. The Mann-Witney test was used to compare continuous variables wit nominal variables. A p value 0.05 was considered significant.
Results. Flow mediated dilation (FMD) was reduced in patients with digital ulcers. The brachial artery diameter at 60 s after cuff deflation had statistical differences (P0.001) between SSc patients with digital ulcers compared to SSc patients without DU or primaryRaynaud phenomenon(RP). End diastolic volume was significantly different between groups (P0.001) suggesting an increase in peripheral resistance in patients with DU. FMD was more reduced in patients with late pattern(Cutolos classification) in capillaroscopy and a statistical differences (P0.001) between early and late pattern (P0.007) was found. Endothelin-1 and ADMA were increased in patients with DU (P0.001) which might explain an excessive vasoconstrictor tone in these patients in association with occlusion of distal digital circulation (avascular areas in capillaroscopy) leading to the reducedFMD in patients with DU. VEGF was increased in SSc patients without DU, we found no difference with primary RP (P0.168). A statistical differences (P0.002) between patients with DU and SSc patients with no DU or with primary RP was found in VEGF. Endoglin was increased in patients with DU (*p*0,001). Patients with Cutolos late pattern in capillaroscopy had a increase in the angiostatic biomarker endoglin in comparison with the other groupsp <0,005).
Conclusion. In our cohort, we identified patients at risk of developing DUs: Ssc 70 positive, decreased FMD and low EDV, late pattern of Cutolos classification, increased ET-1, ADMA and endoglin and a reduced VEGF.Microvascular lesions and an increase in the peripheral resistance associated to endothelial dysfunction and a impaired angiogenesis with an imbalance in favor of increased angiostatic biomarkers may be behind the underlingmechanism of DU.

PS10

IONTOPHORESIS OF TREPROSTINIL AS A TREATMENT OF ISCHEMIC DIGITAL ULCERS IN SYSTEMIC SCLEROSIS: A PROOF-OF-CONCEPT STUDY

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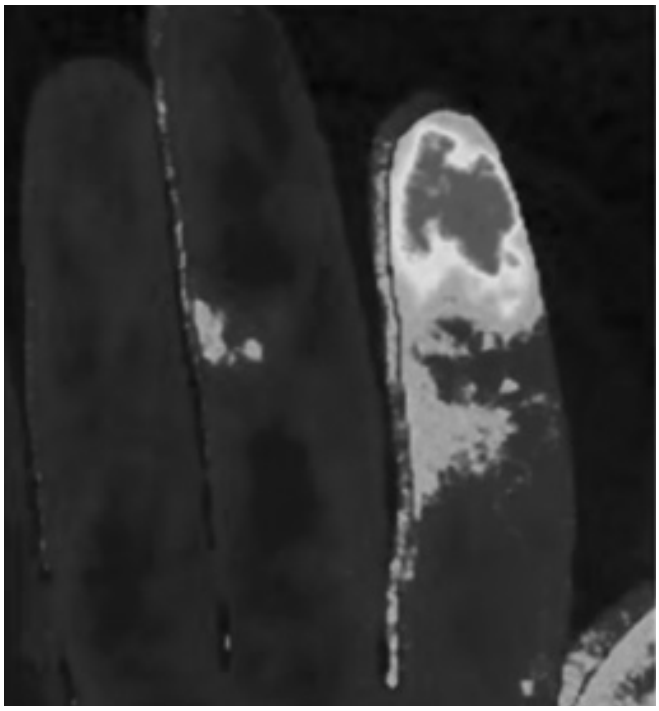
Objectives. Ischemic digital ulcers (DUs) are a complication of systemic sclerosis (SSc). Intravenous prostanoids are the only approved treatment for active DUs but they induce dose limiting side effects. Iontophoresis is a non-invasive drug delivery method that could be an alternative to i.v. treatment. Our primary objective was to evaluate the effect of treprostinil iontophoresis on digital skin blood flow in patients with SSc. First we performed pharmacokinetic and incremental dose studies in healthy subjects.
Methods. Three consecutive studies were conducted: first, twelve healthy volunteers received treprostinil and placebo by iontophoresis on the forearm. Intradermal and plasma drug concentrations were assessed over 8h. Then, a placebo-controlled, double-blind incremental dose study assessed the safety and the effect of treprostinil on the digital skin blood flow of 22 healthy subjects. The highest dose was then compared with placebo in a double-blind study including 12 SSc patients.
Results. The pharmacokinetic study showed that peak dermal concentration was reached at 2h, while the drug was undetected in the plasma. On the finger pad, skin blood flow was higher with treprostinil than at the placebo site with a single dose of 240 mC/cm² in healthy subjects (AUC0-4h were 29703±23460 and 18426±18365%BL.min, respectively; *p*=0.006) as well as in SSc patients (AUC0-4h were 47826±43941 and 30000±27543%BL.min, respectively; *p*=0.023) (Figure). The procedure was safe.
Conclusions. Digital iontophoresis of treprostinil was feasible and well tolerated. It increased skin perfusion in healthy participants and in patients, suggesting that iontophoresis of treprostinil could be tested as a treatment for SSc-related DUs.



Figure

PS11

EVALUATION OF THE EFFICACY OF SILDENAFIL ON TIME TO HEALING IN PATIENTS WITH SCLERODERMA AND ISCHAEMIC DIGITAL ULCERS (SEDUCE): PATIENTS' CHARACTERISTICS AT BASELINE

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Background/Objective. Intravenous iloprost is usually considered in the treatment of ischaemic digital ulcers (DUs) in patients with systemic sclerosis (SSc) despite low evidence on DUs healing in a recent meta-analysis (1). Three small RCTs comparing various PDE-5 inhibitors to placebo suggested DUs healing (2-4), but this was not the primary endpoint.
Methods. SEDUCE was a randomized, placebo controlled, parallel groups study conducted in SSc patients with active fingers ischaemic DUs at inclusion. The aim of SEDUCE was to evaluate the efficacy of a 12-week period with sildenafil 20mg TID or a placebo on time to DUs healing. Patient's characteristics, history of SSc and history of digital ulcerative disease including complications and treatments were collected at baseline.

Results. 84 patients (64 females, age 49.4±13.7 years) were randomized in the study. Phenotypes were diffuse cutaneous SSc in 40 (40.8%), limited cutaneous SSc in 36 (43.4%) and limited SSc in 7 (8.4%). Modified Rodnan skin score was 13.1±8.5. All patients had a history of Raynaud phenomenon (RP) and first non-RP ScS symptom occurred 10.1±7.5 years before baseline. 34 patients had interstitial lung disease (extensive in 8), 4 had history of renal crisis, and 2 had pulmonary hypertension. DLco was 59.0±17.7%. Ischaemic DUs disease evolved for 7.4±6.2 years with a mean number of 2.4±1.8 DUs at baseline. This was the first DUs episode for 8 patients (9.6%) but 51 (61.4%) had a history of 5 or more DUs episodes. 73.5% have had a DUs episode within the 12 previous months. Sympathectomy was noticed in the history in 7 patients and 9 patients have had amputation (self-amputation in 8 and surgical amputation in 2). 49 patients had a history of intravenous iloprost for DUs (15 during the 6 previous months). 39 patients ever had endothelin receptors antagonists that were on-going in 27 (32.5%) at entry in the study. The last randomized patient finished the study in August 2013. The results of the study are expected for the first trimester of 2014.
Conclusion. Patients included in the SEDUCE study had severe active DUs.
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PS12

LASER SPECKLE CONTRAST ANALYSIS TECHNIQUE FOR THE FOLLOW-UP OF DIGITAL ULCERS IN SYSTEMIC SCLEROSIS PATIENTS.

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Background. The decrease of blood perfusion and the risk of digital ulcers are typical aspects of systemic sclerosis (SSc) (1,2). The care of digital ulcers includes both local and systemic treatments (3).
Objective. The aim of this study was to monitor the evolution of digital ulcers with laser speckle contrast analysis (LASCA) technique, in SSc patients treated for ten days with advanced local medications.
Methods. We enrolled five SSc patients with digital ulcers of recent onset (mean age 61±5 years, mean disease duration 7±5 years). At the beginning of the observation (T0) blood perfusion (BP) was evaluated in all patients at the level of the dorsal and palmar surface of whole hand with LASCA (4). Different regions of interest (ROI) were created at the level of fingertip, periungual and ulcer regions. The perfusion was measured in perfusion units (PU) (4). All patients were treated with local dressing, that are elastic and appropriate also for small lesions and curved surfaces. Before applying the dressing the ulcer was cleaned to remove fibrin, to promote granulation of and to prevent the penetration of bacteria into the tissue. The dressing was replaced every 2 days. The patients continued their systemic therapy with acetylsalicylic acid, proton pump inhibitor and antihypertensive drugs. After 10 days of treatment (T1) LASCA was repeated, with the same modalities reported above.
Results. A statistically significant increase of BP was observed between T0 and T1 in the ROIs created at the level of the ulcer area (T0 42.54 PU, T1 58.91 PU, respectively, p=0.04), while no statistically significant diffenence of BP was observed between T0 and T1 at fingertips and periungual levels. We also observed a positive correlation between BP at the level of the fingertip and BP at the level of the ulcer area at both T0 (r=0.92, p=0.03) and T1 (r=0.87, p=0.05). During treatment the ulcers improved and the necrotic tissue was gradually replaced by granulation tissue.
Conclusions. This is the first study evaluating the evolution of blood perfusion at the level of digital ulcers with the LASCA technique. LASCA gives a quantifiable and objective evaluation of perfusion of the ulcer area during treatment.
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Poster Tour 3: *Pulmonary/Interstitial Lung Disease*

PS13

PULMONARY FIBROSIS INDUCED BY BLEOMYCIN IS DRIVEN BY HIGH COLLAGEN V AND TGF-<BETA> SYNTHESIS

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Background. Fibrosing lung diseases are a serious problem to health and are highly ranked among chronic degenerative diseases due to its morbidity. Our group has already observed an important participation of collagen V (COLV) in different types of pulmonary fibrosis, such as systemic sclerosis and idiopathic pulmonary fibrosis. In this context, the better characterization, not only of this extracellular matrix (ECM) component but also of the others ECM components in the experimental models is necessary to identify their interactions. The aim of this study was to evaluate the participation of COLV fibers and TGFβ- in experimental model of pulmonary fibrosis induced by bleomycin (BLM).
Methods. For induction of pulmonary fibrosis, groups of male mice C57Bl/6 (n=5-6), aged 4 to 6 weeks-old with 20-25g, were administered by intratracheal route with bleomycin (BLM) (0.1U/mouse). Sterile saline was used as control. For analysis, mice were sacrificed 14 (early stage) and 21 (late stage) days after induction of pulmonary fibrosis. Lungs were removed for routine histology, immunohistochemistry and histomorphometry. All experimental procedures were performed according to the guidelines of the Ethical Committee of the Faculty of Medicine of University of São Paulo (FMUSP), São Paulo, Brazil (process code 372/11).
Results. A significant higher amount of COLV was found in late stage of BLM when compared to control group (9.74±0.67 vs. 5.14±1.08; p<0.001) and between early and late stages (2.27±0.67 vs. 9.74±0.67; p<0.001). An increase in TGF-β expression was observed in early stage of pulmonary fibrosis when compared to control (22.28±1.05 vs. 1.42±0.49; p<0.001) and also between late stage versus controls (34.86±2.32 vs. 1.42±0.49; p<0.001). A significant difference between the early and late stages of pulmonary fibrosis was observed as well (22.28±1.04 vs. 34.86±2.32, p<0.001). Higher amounts of COLI and COLIII were observed in early (41.56±8.38; 32.09±4.81; respectively, p<0.05) and late stage in BLM (15.26±1.57; 21.69±3.05; respectively, p<0.05) when compared with control group. In addition, higher amounts were observed in total collagen evaluated by 4-hidroxyproline in BLM group when compared to control (33.09 ±5.76, early stage; 42.06±1.55, late stage; p p<0.0003).
Conclusion. The higher amounts of COLV and TGF-β that we observed in the last stage of pulmonary injury produced by BLM probably are important components that contribute to the maintenance of the remodeling process evolution. These data suggest that strategies aimed at preventing the effect of this ECM component may have a greater impact in patients with pulmonary fibrosis. Financial Support: FAPESP, CNPq.

PS14

DISTORTED LUNG FRAMEWORK IS RELATED TO IL-17+ CELLS IMMUNOEXPRESSION IN SYSTEMIC SCLEROSIS

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Background. Although the role of immune dysfunction in the pathogenesis of systemic sclerosis (SSc) is generally accepted, the exact pathways that cause immune dysfunction in SSc remain to be elucidated. Alterations in cellular immunity have been typified by aberrant T cells biology in tissues as well as in the peripheral blood of SSc patients. Investigators have documented an increased number of IL-17+ cells in peripheral blood, in bronchoalveolar lavage and in skin tissue of patients with SSc. More recently, IL-17+ cells have been associated to collagen overexpression in fibroblast of patients with scleroderma.
Objectives. Considering that the prognosis of SSc is associated to lung compromising, the aim of this study was to evaluate the expression of IL-17+ cells in the pulmonary fibrosis process of these patients.
Patients and methods. Lung biopsies were obtained from 14 female patients with SSc (age range 26–56 y, mean 44.1 y): 9 patients had limited SSc, and 5 patients had diffuse SSc according to the American College of Rheumatology criteria. Control samples were collected from necropsies of 6 individuals without pulmonary pathology. The study was approved by the local ethical committee (CAPPesq 0960/08). The samples were fixed in formalin and then embedded in paraffin. The collagen I, III and V deposit in pulmonary interstitium was evalu-

ated by immunofluorescence and quantified by image analysis using the software Image-Pro Plus 6.0. IL17+ cells were immunostained by immunohistochemistry with diaminobendine substrate system and evaluated by the point counting method.
Results. Alveolar septa was 4.7-fold greater in SSc when compared to controls. There was no difference in thickened alveolar septa and collagen content between limited and diffuse SSc. However, in both SSc forms, collagen I was higher expressed than collagen III and V (44.49±0.93% vs. 39.75±2.75%, p=0.011; 44.49±0.93% vs. 40.62±0.702%, p=0.002). The amount of IL-17+ cells in the pulmonary interstitium was higher in SSc patients when compared to controls (3.455±0.36% vs. 1.72±0.19%, p=0.01). Limited and diffuse SSc presented the same amounts of IL-17+ cells.
Conclusions. Distorted lung framework found in SSc is associated to IL-17+ cells immunoexpression, thus suggesting that this cytokine is involved in altered pathway of SSc pulmonary fibrosis and may represent a promissory immune therapeutic target.
Financial support: FAPESP, Federico Foundation.

PS15

DOES MYCOPHENOLATE MOFETIL (MMF) HAVE AN EFFECT ON PULMONARY HEMODYNAMICS? OBSERVATIONS FROM THE PULMONARY HYPERTENSION ASSESSMENT AND RECOGNITION OF OUTCOMES IN SCLERODERMA (PHAROS) COHORT

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Background. Systemic sclerosis (SSc) related pulmonary hypertension (PH) carries a high mortality; with SSc pulmonary arterial hypertension (PAH) having a 4x higher mortality then idiopathic PAH. It is unknown whether immunosuppressant (IS) drugs, particularly mycophenoloate mofetil (MMF), have any effect on vascular remodeling in SSc PH since it has not been formally studied. This analysis looks at the possible effects of MMF in SSc patients who have developed PH.
Methods. PHAROS is a prospective registry designed to provide substantive data to recognize aspects of PH unique to SSc. Patients were stratified by history of MMF or No IS use (no MMF or other immunosuppressant drugs) at the time of the diagnosis of PH by right heart catheterization (RHC). Calculations are derived from non-parametric analyses using Mann-Whitney and Fisher's Exact as applicable followed by regression analyses.
Results. There were 39 SSc patients who had received MMF (mean duration 0.92 years) and 203 patients receiving No IS prior to diagnosis of PH. Patients treated with MMF when compared to the No IS group, were more likely to be younger, have diffuse SSc and have shorter disease duration. Patients treated with MMF had a significantly lower mean pulmonary artery pressure (mPAP) and pulmonary vascular resistance (PVR) with no difference in pulmonary capillary wedge pressure (PCWP) (Table I). However, stratified analyses between diffuse and limited SSc patients on MMF revealed no significant differences in mPAP, PVR, PCWP nor in FVC, TLC, FEV/FVC nor DLCO (Table II). In the group as a whole, MMF (p=0.046) and SSc subtype (p=0.01) were the only independent determinants of mPAP when adjusted for differences in age, FVC and disease duration.

Table I. Comparison between SSc patients on No IS medications and MMF at time of first RHC. Continuous variables are reported as median, interquartile range; categorical values are proportional.

	No IS	MMF	p-value
n	203	39	
Age	60(52.68)	54 (47.63)	*0.0143
Sex (% female)	84%	65%	0.6491
N (%) Limited SSc	144 (71%)	14 (35%)	*<0.0001
Time from 1st SSc Symptom (years)	11.2 (5.3, 21.0)	6.9 (3.0, 10.3)	*0.0004
mPAP	33 (28.44)	29 (25.35)	*0.0016
PVR	355 (242, 692)	222 (162, 344)	*0.0006
PCWP	11 (8.14)	11 (9.15)	0.7036
FVC	78.1 (64.88)	68.9 (48.84)	*0.0298
TLC	76.5 (66.93)	62.8 (47.80)	*0.0002
FEV/FVC	81 (75.87)	87 (81.93)	*0.0048
DLCO	37.5 (30.50)	34.3 (28.39)	0.0929
FVC:DLCO	1.94 (1.6, 2.4)	1.85 (1.4, 2.5)	0.6908
6MWD	338.3 (238, 428)	396.2 (343, 475)	*0.0298

Conclusions. Patients treated with MMF compared to the No IS group had lower mPAP and PVR at time of the diagnosis of PH with no difference between groups in PCWP. Differences in mPAP between groups were not explained by differences in age, FVC, or disease duration. These data suggest that MMF could potentially play a role in pulmonary artery remodeling and modifying the severity of PH. These findings warrant prospective controlled investigations of MMF in SSc PH.

Table II. Comparison of patients on MMF by limited and diffuse subtypes.

	lcSSs on MMF	dcSSc on MMF	p-value
n	14	23	
Age	57.5 (50, 63.8)	51 (40, 63)	0.2185
Sex (% female)	64%	67%	1.0
Time from 1st SSc Symptom (years)	8.4 (6.9, 15.3)	4.1 (2.6, 8.8)	*0.0176
Duration of MMF prior to RHC	0.47 (0.18, 1.6)	0.55 (0.15, 1.2)	0.9694
mRSS	3 (2.5)	16 (7.28)	*<0.0001
PH Meds at Time of RHC	36%	65%	0.1014
mPAP	29 (26.36)	29.0 (25.35)	0.7507
PVR	234 (140, 466)	222 (166, 340)	0.7495
PCWP	11.5 (9.8, 16.5)	11.0 (9.15)	0.7621
FVC	75.9 (57.2, 90.0)	61.7 (45.5, 76.2)	0.1039
TLC	68.9 (54.7, (46.8)	60.3 (46.8, 77.9)	0.1898
FEV/FVC	84.5 (79.0, 88.5)	87.0 (81.8, 93)	0.3181
DLCO	36.2 (31.4, 40.2)	32.5 (25.2, 38.6)	0.2862
FVC:DLCO	2.04 (1.4, 2.6)	1.73 (1.2, 2.3)	0.5168
6MWD	417.1 (362, 502)	388.8 (241, 466)	0.3384

PS16

DEVELOPMENT OF A COMPOSITE OUTCOME MEASURE FOR SYSTEMIC SCLEROSIS-RELATED INTERSTITIAL LUNG DISEASE

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Background. While clinical trials in SSc-ILD have traditionally used FVC as the primary outcome, combining individual outcomes may lead to a more comprehensive measure of treatment response and minimize the risk of type 1 error that can occur when multiple tests are performed on several individual outcomes. The purpose of the present study was to develop a composite outcome measure to assess treatment response in patients with SSc-ILD.
Methods. Using data from the SLS-I study comparing cyclophosphamide treatment versus placebo in 158 patients with SSc-ILD, we entered the following outcome variables into a multivariate regression model to determine which variables had a significant treatment effect at 12 months: change in FVC, TLC, Quantitative lung fibrosis (QLF) by HRCT and mRSS; and the Transitional dyspnea index (TDI). We subsequently combined the variables with significant treatment effects (p<0.05) in a principal component analysis to assess the difference between treatment groups.
Results. Of the 158 patients, 77 had complete outcome data and were included in this analysis. The multivariate model demonstrated significant treatment effects for the following outcome variables (estimate [SE]; p-value): change in FVC (4.4 [1.7]; p=0.01), change in QLF (-12.5 [3.8]; p=0.002), TDI (3.5 [0.8]; p<0.0001). Combining these 3 outcome variables, the first principal component explained 62% of the total variation in these variables. The regression model with the first principal component for these 3 variables as the composite outcome demonstrated a significant treatment effect favoring cyclophosphamide (R2=0.3;β=0.91; p<0.0001). When we combined only change in QLF and TDI, the first principal component explained 70% of the total variation in these outcome variables. The regression model using the first principal component for these 2 variables as the composite outcome also demonstrated a significant treatment effect favoring cyclophosphamide (R2=0.3;β=0.95; p<0.0001).
Conclusion. The composite outcome comprised of change in FVC, change in QLF, and TDI, demonstrated a significant treatment effect favoring cyclophosphamide for the treatment of SSc-ILD. Eliminating change in FVC from the composite outcome did not change the overall treatment effect. Both composite outcome measures demonstrated a more significant treatment effect than using FVC alone as the outcome measure. These findings suggest that combining a patient-reported outcome with a structural outcome into a single measure may serve as a more robust measure of treatment response compared with change in FVC or QLF alone. This model requires validation using another dataset.

PS17

LUNG ULTRASOUND FOR DETECTING INTERSTITIAL LUNG DISEASE IN PATIENTS WITH SYSTEMIC SCLEROSIS

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Objective. To determine whether LUS is a reliable tool for the detection of ILD in patients with SSc compared to the gold-standard, high-resolution computed tomography (HRCT).
Patients and Methods. Consecutive patients diagnosed with SSc (ACR 1980), whom as part of their clinical evaluation had undergone a HRCT for the past three months and did not have clinical signs of right heart failure and active pulmonary infection were studied.
A blind operator of clinical and tomographic medical history of patients achieved the LUS for the detection of B-lines with the method described by Gargani *et al*. using a 3.5 MHz convex transducer. The sum of artifacts found in anterolateral and posterior chest results in a score that measures the degree of interstitial lung involvement. A study of more than 10 B-lines was taken as positive.
It was considered that HRCT was positive for ILD when had at least ground-glass opacity, lung fibrosis or honeycombing. The HRCT's were also objectively evaluated by an expert using the scoring proposed by Warrick *et al*. (0 to 30).
Results. A total of 34 patients were included, with a mean age of 51 years and a disease duration of 6 years on average. The 55% of the patients were limited disease and the 45% diffuse.
There was a statistically significant difference in the number of B-lines among patients with or without ILD on HRCT (113,04±81,05 vs 11,90±9,33; p<0,0001). A statistically significant positive linear correlation was found between the number of B-lines and the Warrick score (r 0,5569, p<0,0006). Also a significant negative correlation between LUS score and forced vital capacity was found (r -0.5509, p<0.0070).
The correlation between LUS and HRCT for individual patients was 85%, with a sensitivity of 100% (NPV 100%) and specificity of 50% (PPV 82.76%). A ROC curve analysis demonstrated the analytical relationship between the number of B-lines and the presence of ILD at HRCT (AUC 0.994, 95% CI 0.885 to 1.000, p<0.0001). A total number of B-lines >22 had a sensitivity of 100% and a specificity of 90%.
Conclusions. Lung ultrasonography is a valid method for the detection of ILD in SSc. Its high sensitivity and negative predictive value make it a powerful screening tool in these patients. However, its main limitation is the lack of specificity because B-lines may also be detected in cardiogenic pulmonary edema and parenchymal infectious sequelae.

PS18

INTERSTITIAL LUNG DISEASE IN SYSTEMIC SCLEROSIS: CLINICAL PRESENTATION AND COURSE DIFFERENCES BETWEEN PM/SCL AND SCL-70 ANTIBODIES

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Objectives. To describe the characteristics of patients with Interstitial Lung Disease related to Systemic Sclerosis (ILD-SSc), with positive anti-PM/Scl antibody compared to a group with anti-Scl-70.
Methods. Sixty-three Spanish patients with ILD-SSc were selected in a retrospective observational study. ILD diagnosis was based in high-resolution computed tomography (HRCT), 14 had positivity for anti-PM/Scl antibody and 49 for anti-Scl-70. Clinical assessments, including pulmonary function test, were collected. Non-parametric tests and Kaplan-Meier curves were performed for statistical analysis.
Results. There were significant differences between anti-PM/Scl and anti-Scl-70 patients attending the first non-Raynaud phenomenon symptom at onset of SSc. Arthritis and puffy hands were the first symptoms in 57.1% of anti-PM/Scl patients (p<0.001), whereas the thickening of skin was in the 55.1% of anti-Scl-70 group (p<0.001). Diffuse subset was higher in anti-Scl-70 antibody (69.4% vs. 7.1%, p<0.001). There were no differences in age at ILD diagnosis nor the basal HRCT or forced vital capacity (FVC). Scl-70 patients had more peripheral vascular disease (100% vs. 78.6%, p=0.009) and gastrointestinal involvement (57.1% vs 88.9%, p<0.001). Inflammatory myopathy was associated to PM/Scl antibody (71.4% vs 6.1%, p<0.001). Regarding the lung course, the time of follow-up since ILD diagnosis was similar in both groups. Any grade of dyspnea was less commonly presented in anti-PM/Scl patients (50.0 vs 73.4%, p=0.03). An increment of 1.1% in FVC% predicted was documented in the PM/Scl group, while in the anti-Scl-70 group a decrease of 10.9% was observed (p=0.004). PM/Scl patients had less percentage of significant worsening in FVC% (15.4% vs. 52.4%, p=0.01), with higher proportion of a significant improvement in FVC% than Scl-70 group (30.8% vs. 7.1%, p=0.01). Severe restrictive pattern (FVC < 50%) during follow-up was less frequently documented in PM/Scl patients (7.7% vs 42.9%, p=0.02). The progression-free survival (PFS) which endpoint was defined as death or a decline greater than 10% in FVC%, was higher in anti-PM/Scl patients after 10 years from diagnosis of ILD (76% vs 29%, p=0.04)
Conclusions. We have found that PM/Scl antibody is related to more inflammatory myopathy and less peripheral vascular disease and gastrointestinal involvement. The anti-PM/Scl patients had a stabilization of FVC during follow-up. Even a third part had an improvement higher than 10% in FVC. This group presented less severe restrictive pattern, and a better progression-free survival. Results in our study have shown similar outcomes to the previously published, which highlights that ILD-SSc has a different behaviour depending on the immunologic profile.

PS19

LONG TERM FOLLOW-UP AFTER INTRAVENOUS CYCLOPHOSPHAMIDE PULSE THERAPY FOR SCLERODERMA INTERSTITIAL LUNG DISEASE: RESULTS OF A SINGLE CENTER EXPERIENCE

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Objectives. To analyze pulmonary function tests (FVC, DLCO), pulmonary artery pressure (PAP, ECHO-Doppler), and skin thickening (modified Rodnan' skin score, mRSS) at years 1,4,7 of follow-up after IV cyclophosphamide (CYC) treatment for active scleroderma interstitial lung disease (SSc-ILD: ground glass and/or pulmonary fibrosis on chest HRCT and reduction in FVC and/or DLCO for more than 10% during 2 consecutive visits).
Results. Among 230 SSc patients at our EUSTAR site, 42 had an active ILD. 28 patients started CYC before year 2007 and 17- before 2004). Age, disease duration, follow-up, and cumulative CYC doses were (mean ± SD) 50.7±12.7 years, 16.3±17.9 months, 6.5±6 years, 8.96±3.8 G. Eight patients died (6 -due to SSc). Three patients developed complications: 2-pneumonia, 1-hepatitis B reactivation and Kaposi sarcoma, 1-premature menopause. During the first year FVC remained stable, DLCO and mRSS declined significantly. Main changes in FVC, DLCO, and mRSS were observed in first 4 years after CYC treatment with mild additional reduction in the follows years. PAP elevation was more prominent between 4th and 7th years. Mean annual changes (in %) in FVC, DLCO, mRSS, and PAP during 0-4 years and 4-7 years were: FVC 3.2 and 0.4 (p<0.004), DLCO 4.6 and 0.9 (p<0.001), and mRSS 1.8 and 0.2 (p<0.002). Among presenting features (cough, dyspnea, lung crepitus, acute phase reactants, autoantibodies) only elevated CK correlated with FVC, DLCO and PAP (p=0.04, p=0.026, p=0.028) changes. Cumulative doses of CYC higher than 6G had no additional effects on changes in variables. Highest annual reduction in FVC and DLCO during first 4 years correlated with mortality (p=0.022).
Conclusions. In SSc-ILD CYC infusions stabilized FVC during the 1st year but did not prevent further FVC and DLCO reduction as well as PAP elevation. CYC rapidly and significantly improved mRSS. Cumulative doses of CYC above 6G had not additional influence on FVC, DLCO, and mRSS reduction. Elevation of PAP became significant between 4th and 7th years of follow-up. CYC may be an effective induction therapy for SSc-ILD especially regarding lung volumes. The effect of CYC was lost in next years of follow-up. In the light of possible side effects it is a need for maintenance therapy with alternative DMARD after stabilization of pulmonary function tests with CYC. High annual rated of FVC and DLCO reduction might be an indication for more aggressive treatment early in the course of SSc-ILD.

Poster Tour 4: *Pulmonary Arterial Hypertension*

PS20

PULMONARY ARTERIAL HYPERTENSION (PAH) IN A CONTEMPORARY DRUG REGISTRY: RESULTS OF THE VOLT STUDY WITH AN EMPHASIS ON PAH ASSOCIATED WITH CONNECTIVE TISSUE DISEASE (CTD)

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VOLT (VOL-ibris Tracking) was an observational, multicenter registry, collecting safety information on the endothelin receptor antagonist ambrisentan (AMB) use in clinical practice.

Methods. The primary objective was to assess the overall safety profile of ambrisentan in clinical practice. The study was powered to detect a doubling of aminotransferase elevation >3x the upper limit of normal (ULN), from 1.5% to 3% per annum. Information on adverse events (AEs), AMB exposure and reasons for stopping, use of other PAH medications, functional class, hospitalisations and death was also collected.

Results. Demographics are shown in Table I. The population was in line with PAH populations seen in registries and similar between the overall population and the CTD subgroup. Cumulative overall exposure was 2188 patient years, with a mean of 2.2 years/patient in the overall population, and 2.0 years/patient in the CTD-population. Exposure-adjusted rate of aminotransferase elevations >3xULN (ALT and/or AST, highest value given) was in line with the assumed background rate, and similar between the overall population (2% (95% CI: 1.5%,2.7%) and the CTD population (2.8% (95% CI: 1.5%,4.8%). The most common AEs reported (>10%) were oedema (24%), dyspnoea (15%), anaemia (12%) and heart failure (12%), and was similar in the CTD population (though 10% of CTD patients also experienced pneumonia). Hospitalisations and death occurred in 30% and 22% respectively of the overall population, and 26% and 27% respectively of the CTD-population.

Conclusions. The population recruited is consistent with a real life PAH population. The results suggest that the safety profile of ambrisentan in clinical practice is similar to that seen in randomised clinical trials, and that ambrisentan in CTD-PAH has a similar safety profile to the overall population.

Table I. Baseline Demographics.

Characteristic	Overall Population (n=998)	CTD population (n=238)
Mean Age	59.5	62.3
Female	667 (67%)	207 (87%)
Race:		
White/Caucasian	849 (85%)	207 (87%)
Missing	113 (11%)	22 (9%)
Other	36 (4%)	9 (4%)
Years since PAH diagnosis	2.9 years	2.4 years
Diagnosis of PAH		
Idiopathic PAH	446 (45%)	Limited Systemic Sclerosis (CREST) 124 (52%)
Heritable PAH	8 (<1%)	
PAH associated with underlying diseases	418 (42%)	Systemic Lupus Erythematosus 26 (11%)
		Mixed CTD 18 (8%)
Missing	126 (13%)	Missing 70 (29%)
Baseline Functional Class	N=990	N= 235
I	22 (2%)	5 (2%)
II	258 (26%)	65 (28%)
III	642 (65%)	148 (63%)
IV	68 (7%)	17 (7%)

PS21

AUTOANTIBODY PROFILE IN SYSTEMIC SCLEROSIS ASSOCIATED PULMONARY HYPERTENSION

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Objectives. Pulmonary hypertension (PH) is a severe complication of systemic sclerosis (SSc), affecting around 10% of patients. A recent meta-analysis showed an overall 3-year survival of 52% (1). The impact of autoantibody on clinical phenotype of PH-SSc patients is not completely established. This study aimed to describe and compare the type of PH and hemodynamic characteristics between different profiles of autoantibody in SSc patients.

Methods. Five hundred and forty tree patients diagnosed with PH on right heart catheterisation (mean pulmonary arterial pressure mPAP >=25mmHg) between 1998 and 2012 were retrieved from our local database. Anti-nuclear antibody (ANA) profiles (n=457) were retrieved from clinical immunology records (missing data in 86 patients).

Results. The distribution of ANA among SSc-PH patients was as follows: anti-centromere antibody (ACA) 39%, anti-topoisomerase I (ATA) 12%, anti-RNA polymerase III (ARA) 6%, anti-U1RNP 6%, anti-U3RNP 5%, anti-PM/Scl 3%, anti-Th/To 3%. Seven percent of patients had multiples specificities or anti-dsDNA or anti-Ro/SSa alone. Fifteen percent were ANA positive in immunofluorescence and ENA (extractable nuclear antigen) negative. Five percent were ANA negative. Types of PH in patients with different ANA are presented in Figure 1. In PAH-SSc patients (n=308), significant differences were found between ANA groups for: age at PAH diagnosis (p<0.001), mPAP (p=0.025), FVC (p<0.001) and DLCO (p<0.001). Patients with ACA, ATA, ENA negative and ANA negative had the highest means of age at PAH diagnosis; patients with anti-U3RNP and anti-PM/Scl had the lowest. Patients with ACA had a higher FVC than ATA and ENA negative patients (p<0.05). Patients with ATA and ENA negative had the lowest DLCO. There was a trend for lower mPAP in ATA than in ANA negative patients (p=0.091). No other significant difference in hemodynamic characteristics was found between PAH-SSc patients.

Conclusion. PAH was the cause of PH in more than half of patients with ACA, anti-U3RNP anti-Th/To, ENA negative and ANA negative. In PAH-SSc, there were differences in age at PH diagnosis and pulmonary function tests between ANA groups. However, no difference was found in hemodynamic characteristics.

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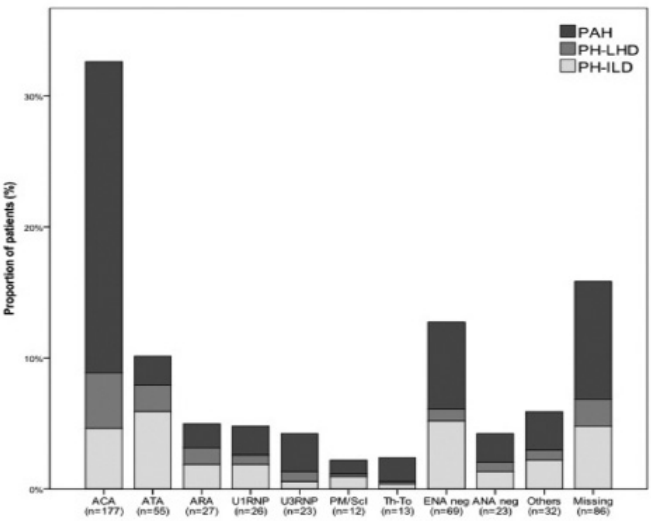

Fig. 1.

PS22

RELEVANCE OF THE 6-MINUTE WALKING TEST IN ASSESSING THE SEVERITY OF PULMONARY ARTERIAL HYPERTENSION ASSOCIATED WITH SYSTEMIC SCLEROSIS, WITHOUT INTERSTITIAL LUNG DISEASE

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Introduction. In patients with idiopathic pulmonary arterial hypertension, 6-minute walking test (6MWT) correlates well with hemodynamic parameters and is a robust prognosis factor. In PAH associated with systemic sclerosis (SSc-PAH) however, data are more scarce and still a matter of debate. Various comorbidities caused by the underlying systemic disease may be confounding factors. Moreover, no study has evaluated the correlation between the 6MWT and the hemodynamics (*i.e.* the gold standard test to assess the severity of PAH) in this population yet. Our study aimed to assess whether there is a correlation between the 6MWT and the hemodynamic parameters measured during the right heart catheterization (RHC), in SSc-PAH patients without interstitial lung disease (ILD).
Methods. We included 75 patients with SSc-PAH and without ILD on chest HRCT, prospectively enrolled in the French PAH Network. Several data were collected at baseline regarding the clinical status (age, sex, BMI, NYHA class), the 6WMT (total distance, HR and deltaHR,SaO2 and deltaSaO2, Borg score), the RHC (mRAP, mPAP, sPAP, dPAP, CO, CI, PVR, TPR, systolic stroke volume), the PFT (FEV1, FVC, TLC, DLCO/VA, PaO2, PaCO2) and the TTE. The correlation of the 6MWT total distance with each hemodynamic parameter, but also with other data, was studied by linear regression.
Results. Univariate analysis showed a statistically significant correlation between the 6MWT total distance (expressed in meters and in percentage of normal value) and all the RHC hemodynamic parameters, especially the mPAP (R^2=0.10, p=0.0045), CI (R^2=0.20, p<0,0001) and PVR (R^2=0.18, p=0,0001). A similar correlation was also found between 6WMT total distance (when expressed in percentage of normal value) and the NYHA class, FEV1 and FVC.
In multivariate analysis, the 6WMT total distance (expressed in meters) was significantly and independently correlated with the CI, dPAP, FVC, age and NYHA classes 3 and 4. Those 5 parameters accounted for 46% of the 6MWT total distance, the CI explaining the majority of the distance (R^2=0,24).
Discussion. To our knowledge, this study is the first to prove a correlation between the 6MWT total distance and the hemodynamic parameters of PAH severity, in SSc-PAH patients without ILD. It further establishes the relevance of this test in assessing the severity of the PAH in this population.
Conclusion. Although potentially confounding comorbities are frequent, the 6MWT remains a relevant way to assess the severity of the PAH in SSc patients without ILD. However, other factors are probably involved in the 6MWT total distance, since the studied parameters accounted for only half of it.

PS23

COST SAVINGS WITH A BIOMARKER-BASED SCREENING ALGORITHM FOR PULMONARY ARTERIAL HYPERTENSION IN SYSTEMIC SCLEROSIS

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Background and aim. Most screening models for pulmonary arterial hypertension (PAH) in systemic sclerosis (SSc) use transthoracic echocardiography (TTE) as a 'first tier' test. TTE is costly, requires expertise, and is limited by the absence of a TR jet and inestimable sPAP in up to 30% of patients. We have recently derived and validated a novel screening algorithm for SSc-PAH, based on serum NT-proBNP measurement combined with pulmonary function testing (PFT), which is highly sensitive and easy to use. In this study, our objective was to compare the accuracy and cost of SSc-PAH screening using this new algorithm (ASIGnew), with an existing TTE-based algorithm (ASIGold).
Methods. We included consecutive patients enrolled into the Australian Scleroderma Cohort Study who had undergone their first screening for pulmonary arterial hypertension using TTE and PFT between 2007 and 2012, and in whom serum had been collected for NT-proBNP measurement using the Elecsys immunoassay, at the time of screening or right heart catheterization (RHC). The existing Australian Scleroderma Interest Group SSc-PAH screening algorithm (ASIGold) recommends RHC for patients with sPAP >=40 mmHg on TTE or DLCO <=50% with FVC >85% predicted on PFT. In ASIGnew, patients screen positive if either DLCO <70% and FVC/DLCO >=1.8 on PFT, or NT-proBNP level is >=210 pg/ml. All patients who screen positive then undergo TTE followed by RHC. PAH was defined based on RHC as mPAP >25mmHg at rest and PCWP <15mmHg. The cost of the tests was obtained from the Australian medical benefits schedule. We compared ASIGold and ASIGnew in terms of (i) the number of TTE and RHC required to diagnose one case of PAH and (ii) the total cost of screening, and the cost of diagnosing one case of PAH.
Results. The results of the application of the algorithms to 643 patients are presented in Table I. ASIGold missed 1 case of PAH detected by ASIGnew. ASIGnew resulted in 64% fewer TTE and 10% fewer RHC. ASIGnew resulted in a cost saving of $88,084 for the 'first' PAH screen in this cohort of 643 patients. This is a cost saving of $1,011.50 per case of PAH diagnosed.
Conclusion. Our biomarker-based SSc-PAH screening algorithm has better accuracy that the existing algorithm, reduces the number of TTE and RHC required, reduces the overall costs of screening, and reduces the cost of diagnosing each case of PAH.

Table I. $ASIG_{OLD}$ and $ASIG_{NEW}$ algorithms applied to 643 consecutive patients with SSc. NNS: number needed to screen. All costs are in Australian Dollars.

	$ASIG_{OLD}$	$ASIG_{NEW}$
Total number of patients	643	643
Number (%) screen +	256 (40%)	231 (36%)
% screen + with PAH on RHC	45%	50%
TTE required	643	231
RHC required	256	231
NNS to get one screen +	2.50	2.78
Number of RHC to diagnose one case PAH	5.50	5.56
Total cost of screening and diagnosis	$851,917	$727,833
Cost of diagnosis of one case of PAH	$7,311.70	$6,300.20

PS24

VALUE OF SYSTOLIC PULMONARY ARTERIAL PRESSURE AS A PROGNOSTIC FACTOR OF DEATH IN SYSTEMIC SCLEROSIS EUSTAR POPULATION

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Objective. To assess the prognostic value of systolic pulmonary artery pressure (sPAP) estimated by echocardiography in the multinational EULAR Scleroderma Trial and Research (EUSTAR) cohort.
Methods. Data of patients with echocardiography documented between January 1st 2005 to December 2011 31st were extracted from the EUSTAR database. Stepwise-forward multivariable statistical Cox PH analysis was used to examine the independent effect on survival of selected variables.
Results. Based on our selection criteria, 1476 patients were included in the analysis. 87% of patients were females, mean age was 56.3±13.5 years and 31% had diffuse systemic sclerosis (SSc). Mean duration of follow-up was 2.0±1.2 years (median 1.9 years). Taking index sPAP < 30 mmHg as reference, hazard ratio for death were 1.67 [95%CI 0.92-2.96] if index sPAP was between 30-36 mmHg, 2.37 [1.14-4.93] for sPAP between 36-40 mmHg, 3.72 [1.61-8.60] for sPAP between 40-50 mmHg and 9.75 [4.98-19.09] if sPAP was >50 mmHg. In a multivariable Cox model, sPAP and DLCo were independently associated with the risk of death (HR=1.833; 95%CI=[1.035-3.247] and HR=0.973; 95%CI=[0.955-0.991] respectively).
Conclusion. An estimate sPAP above 36 mmHg at baseline echocardiography was significantly and independently associated with a reduced survival, regardless the presence or not of pulmonary hypertension based on right heart catheterization.

PS25

ABERRANT BMP SIGNALLING MAY CONTRIBUTE TO PULMONARY COMPLICATIONS IN A TGF DEPENDENT MURINE MODEL OF SCLERODERMA.

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Background. Patients with pulmonary arterial hypertension associated with scleroderma (PAH-SSc) have a poorer prognosis compared to those with idiopathic (iPAH) or heritable (hPAH) forms of the disease, but the mechanisms that contribute to the development of PAH-SSc remain unclear. BMPRII mutations with concomitant effects on BMP signalling are an established cause of hPAH and some iPAH but these are not present in PAH-SSc.
Method. We investigated BMP signalling in the lung in the TRIIk-fib model of PAH-SSc in which TGF signalling is upregulated. The TRIIk-fib mouse develops a structural pulmonary vasculopathy with smooth muscle hypertrophy and raised right ventricular pressures. Experiments were performed on whole lung isolates and explant cultured fibroblasts (n=6) from the TRIIk-fib mouse and compared with wildtype littermate controls. Structural and biochemical analysis of components of the TGF superfamily and downstream signalling pathway was investigated by Western blot and immunohistochemistry and confirmed using qPCR measurement. Migration assays investigated the effects of PDGF-BB on lung fibroblasts from TRIIk-fib and WT controls (n=3). Confirmatory biochemical and functional studies on scleroderma fibroblasts were also performed.
Results. The TRIIk-fib model has increased levels of pSmad 2/3, indicative of enhanced TGF signalling. Consistent with an imbalance in the TGF/BMP axis we observed a significant reduction in BMPRII protein expression in the TRIIk-fib model, both in whole lung isolates ($p<0.05$), and explant cultured fibroblasts ($p<0.05$). A reduction of BMPRII was also observed in explant cultured lung fibroblasts from SSc patients compared to healthy controls. Murine fibroblasts exhibited a blunted response to BMP ligands ($p<0.05$). TRIIk-fib lung fibroblasts and SSc fibroblasts also exhibited enhanced migratory response compared controls ($p<0.05$).
Conclusion. In hPAH 70% of patients possess mutations in the BMPRII gene, which leads to a reduction in functional cell surface associated receptor. Here we demonstrate the TRIIk-fib transgenic murine model of PAH-SSc exhibits reduced expression of BMPRII as a reciprocal response to increased TGF signalling, with associated downstream signalling alterations independent of mutations in the BMPRII. We also show a similar trend in clinical material with a reduction of BMPRII in SSc fibroblasts and whole lung histology. Interestingly TRIIk-fib and SSc fibroblasts exhibit a heightened migratory response to PDGF-BB. Collectively our data suggests loss of BMPRII expression by non-genetic means may contribute to the development of PH in the TRIIk-fib mouse model by promoting an imbalance in the TGF/BMP axis and a similar mechanism may contribute to PAH in scleroderma.

PS26

CHARACTERISATION OF LATE-OUTGROWTH ENDOTHELIAL PROGENITOR CELLS FROM SYSTEMIC SCLEROSIS PATIENTS

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Introduction. Vascular complications associated with systemic sclerosis (SSc) including pulmonary arterial hypertension (PAH-SSc), result from endothelial damage and loss of barrier function. The causes of endothelial dysfunction are unclear, but the integrity of the endothelium is likely to be significantly diminished in SSc. Endothelial progenitor cells (EPCs) derived from peripheral blood mononuclear cells (PBMCs) express endothelial and haematopoietic markers. It is thought they home to sites of vascular injury and differentiate into endothelial cells and restore the barrier. In SSc patients circulating levels of EPCs are reduced. This study aimed to: (i) develop a robust method to isolate and grow healthy control (HC) and SSc EPCs from PBMCs. (ii) Compare the cellular functions of EPCs to mature endothelial cells.
Methods. Peripheral blood was taken from HC (n=10) and SSc donors (n=10). EPCs were cultured from PBMCs, and EPC colonies grown to passage 4. EPCs and human pulmonary artery endothelial cells (hPAECs) were seeded into transwell inserts and grown to confluence. Cells were incubated with TNF-α (10ng/

ml), and their capacity to form biological barriers and support immune cell influx was assessed using FITC-albumin (0.5mg/ml) and neutrophil transmigration. We further assessed the responses of EPCs to TNF-α stimulation by ELISA to quantify pro-inflammatory cytokine release.
Results. We demonstrate that EPCs form biological barriers with similar capabilities as mature hPAECs in vitro. TNF-α significantly enhanced permeability of EPCs (p<0.05) and hPAECs (p<0.05) monolayers. Consistent with EPCs possessing similar cellular activities as mature endothelial cells, TNFa stimulated neutrophil transmigration in monolayers of EPCs (p<0.05) and hPAECs (p<0.05) and enhanced the secretion of IL-8 in both EPCs (p<0.01) and hPAECs (p<0.05). We sought to determine the frequency of EPC colony formation from PBMCs and found no significant difference in the capacity to form EPC colonies in HC and SSc patient PBMCs.
Discussion. We have developed a robust method for isolating EPCs from PBMCs. We have demonstrated that endothelial progenitors can maintain an endothelial barrier consistent with that observed by mature hPAECs *in vitro*. We have established that EPCs respond to TNF-α in a similar manner to mature PAECs, secreting pro-inflammatory cytokines such as IL-8 and supporting neutrophil transmigration. We have shown no significant difference in the capacity of PBMCs from SSc patients to form EPC colonies compared to healthy control donors. The biological function and importance of EPCs from SSc patients in vasculopathy, restoration and maintenance of the endothelial barrier function remains unclear.

PS27

AUTOANTIBODIES TARGETING ANGIOTENSIN TYPE 1 AND ENDOTHELIN TYPE A RECEPTORS AS BIOMARKERS AND MEDIATORS OF SYSTEMIC SCLEROSIS ASSOCIATED PULMONARY ARTERIAL HYPERTENSION

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Objective. Systemic sclerosis (SSc) associated pulmonary arterial hypertension (PAH) portends worse outcome than other forms of PAH. Vasoconstrictive and vascular remodeling actions of Endothelin-1 (ET-1) and Angiotensin II (Ang II) via endothelin receptor type A (ETAR) and angiotensin receptor type-1 (AT1R) are implicated in PAH pathogenesis in general. We hypothesized that autoantibodies (Abs) targeting and activating AT1R and ETAR may contribute to SSc-PAH pathogenesis and tested their functional and biomarker relevance.
Methods and Results. Anti-AT1R and -ETAR Abs detected by ELISA were significantly higher and more prevalent in patients with SSc-PAH (n = 81) and connective tissue disease(CTD)-associated PAH (CTD-PAH; n = 110) as compared to other forms of PAH/PH (n = 106). High anti-AT1R and anti-ETAR Abs predicted development of SSc-PAH and SSc–PAH-related mortality in a prospective analysis. Both autoantibodiesAbs increased endothelial cytosolic Ca2+ concentrations in isolated perfused rat lungs which could be blocked by respective specific receptor antagonists. Stimulation of third to fourth-generation intralobar pulmonary rat artery ring segments in a small vessel myograph with anti-AT1R and anti-ETAR Abs increased vasoconstrictive responses to Ang II and ET-1 and implicated cross-talk between both pathways demonstrated by reciprocal blockade with respective antagonists. Transfer of SSc-IgG containing both autoantibodies into healthy C57Bl/6J mice lead to more abundant vascular and epithelial alpha smooth muscle actin expression and inflammatory pulmonary arteriopathy.
Conclusions. Anti-AT1R and ETAR Abs discriminate SSc-PAH/CTD-PAH from other forms of PH and serve as predictive and prognostic biomarker of SSc-PAH. Both antibodies contribute to SSc-PAH via increased vascular endothelial reactivity and induction of pulmonary arteriopathy.

Poster Tour 5: *Cardiac*

PS28

SUBCLINICAL BIVENTRICULAR SYSTOLIC FUNCTION IS IMPAIRED IN PATIENTS WITH SYSTEMIC SCLEROSIS: A SPECKLE TRACKING-BASED ECHOCARDIOGRAPHIC STUDY

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Background/Purpose. Myocardial involvement is associated with poor prognosis in patients with systemic sclerosis (SSc). In the present study we aimed to evaluate subclinical left ventricular (LV) and right ventricular (RV) systolic dysfunction in SSc patients without any cardiovascular disease, by using a strain imaging method, "speckle tracking echocardiography" (STE).
Methods. Thirty-six SSc patients were screened, 7 patients were excluded because of ischemic heart disease. We studied 29 patients with SSc (diffuse/ limited: 15/14) and 20 age and sex-matched healthy controls(HC), without any cardiac disease and with preserved LV-EF. Conventional echocardiography and STE-based strain imaging were performed to assess biventricular deformation analyse. Association with anti-Scl 70 was sought in patients with SSc.
Results. In SSc patients (Female/Male: 25/4) the mean age was 47.7 years. Anti Scl-70 was positive in 13 (44.8%) patients. Left ventricular conventional echocardiographic measurements (LV end diastolic diameter, LV end systolic diameter and LV EF) were similar between SSc and HC. Regarding RV conventional parameters, right atrium was significantly enlarged, tricuspidal annular plane systolic excursion (TAPSE) was decreased and systolic pulmonary artery pressure was increased in SSc compared to HC (p<0.001). Both LV and RV longitudinal peak systolic strain/ strain rate were significantly impaired in SSc, demonstrating subclinical LV and RV systolic dysfunction (p<0.001) (Table).
We obtained significant positive correlation between TAPSE and RV longitudinal peak systolic strain/strain rate (r=0.744 and r=0.706, respectively, p=0.0001). Systolic PAB was negatively correlated with both LV and RV longitudinal peak systolic strain/strain rate (LV: r=-0.552 and r=-0.637, respectively, p<0.001 and RV: r=-0.547 and r=-0.638, respectively, p=0.001). Anti Scl -70 positive patients had impaired LV longitudinal peak systolic strain and strain rate values, compared to the others, however the difference did not reach statistical significance (13.01±1.26 % to 13.04±1.90 %, p=0.96 for strain; 0.30±0.06 1/s to 0.31±0.15 1/s, p=0.79 for strain rate).
Conclusion. SSc is associated with myocardial systolic dysfunction. Deformation analysis by STE-based strain imaging is a novel promising modality allowing for detailed measurement of early deterioration in biventricular systolic function in patients with SSc.

Table. Conventional echocardiography and Speckle tracking echocardiography (STE) results of SSc patients and healthy controls.

	SSc	HC	*p* value
Right atrium (cm)	3.71±0.30	3.43±0.20	0.004
TAPSE (cm)	2.01±0.41	2.82±0.54	0.0001
Systolic PAB (mmHg)	34.13±8.96	22.07±3.87	0.0001
LV longitudinal peak systolic strain (%)	13.3±1.51	18.87±3.78	0.0001
LV strain rate (1/s)	0.31±0.11	1.77±0.54	0.0001
RV longitudinal peak systolic strain (%)	11.83±1.93	14.19±2.29	0.001
RV strain rate (1/s)	0.30±0.18	2.66±0.4	0.0001

Values were presented as mean +SD. 7APSE: tricuspidal annular plane systolic excursion; PAB: pumonary artery pressure; LV: left ventricle; RV: right ventricle.

PS29

IMPAIRED FUNCTIONAL CAPACITY IN PATIENTS WITH SYSTEMIC SCLEROSIS IS RELATED TO RIGHT VENTRICLE DYSFUNCTION

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Objective. Systemic sclerosis (SSc) is characterised by cardiovascular manifestations, which may affect patient's clinical symptoms. The study was designed to assess whether the impaired exercise tolerance in patients with SSc without overt cardiopulmonary complications is related to the left ventricle (LV) or right ventricle (RV) dysfunction and vascular remodeling.
Methods. Forty seven patients (F/M 36/11; age 51.7±9.9) with diagnosed SSc and clinical symptoms of the heart dysfunction (NYHA I/II) were enrolled into the study. In all the patients, pulmonary arterial hypertension (PAH), pulmonary fibrosis, left ventricle (LV) systolic dysfunction and valvular heart diseases were excluded. The following tests were performed: echocardiography, ultrasound vascular indexes: flow mediated dilatation, nitroglycerin mediated dilatation and arterial tonometry parameters: pulse wave velocity, pulse pressure and augmentation index. The above indexes were related to the 6 minute walk test (6MWT) results.
Results. The 6MWT mean value was 440.0±72m. The LV diastolic dysfunction parameters did not correlate with 6MWT. The RV systolic dysfunction (fraction area change<32%), decreased tricuspid annular plane systolic excursion (TAPSE <20mm) or low peak systolic velocity of lateral tricuspid annulus (TDI: RV S' <20cm/s) were found in 1 (2%), 5 (11 %), 43 (92%) patients, respectively. The 6MWT values correlated with TAPSE (r=0.318, p=0.030) and TDI: RV S' (r=-0.295, p=0.048). There were no significant correlations between ultrasound and arterial tonometry parameters and 6MWT values.
Conclusion. After exclusion of typical causes of low exercise capacity in SSc, the shortened 6MWT distance observed in this group seems to be related to the RV systolic impairment, which supports application of regular echocardiographic screening for early detection of the heart involvement in SSc patients.

PS30

MMP12 CONTRIBUTES TO HEART AND SKIN FIBROSIS IN ANGIOTENSIN II MODEL

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Background. MMP12 is a macrophage-secreted elastase that is highly elevated in the serum and tissue of SSc patients. Angiotensin II (AngII), a vasoconstrictive peptide, is a well-known inducer of heart and skin fibrosis. The goal of this study was to characterize the extent of vascular injury and to investigate the contribution of MMP12 in the AngII model of skin and heart fibrosis.
Methods. AngII was administered continuously over 14 days by subcutaneous osmotic pump in C57Bl and MMP12KO mice. Collagen content measurements were performed by Picrosirius Red (heart) and Gomori's Trichrome (skin) staining and hydroxyproline assays. Apoptosis was evaluated by IHC staining of cleaved Caspase-3. Analysis of injured endothelial cells was performed by IHC staining of vWF, THBS1 and MMP12. Protein levels of vWF, THBS1 and MMP12 in human dermal microvascular endothelial cells (HDMECs) in response to AngII were evaluated by Western blot. The activation of perivascular cells was performed by IHC and immunofluorescence staining of aSMA, NG2, PDGFRβ, CD45 and Collagen I.
Results. Cleaved Caspase-3 staining showed moderately increased apoptosis in heart and skin of AngII treated mice. Immunostaining in the heart and skin of AngII treated mice showed increased expression of vascular injury markers: vWF, THBS1 and MMP12. Protein levels of vWF, THBS1 and MMP12 were also increased in AngII treated HDMECs. PDGFRβ-positive cells colocalized with vessels only in control mice, but were greatly increased in numbers in the heart and skin of AngII mice. Furthermore, in the heart Collagen I producing cells were also positive for PDGFRβ and NG2, while in the skin, in addition to PDGFRβ and NG2 expression, were also positive for aSMA. Additionally, there was an increased number of fibrocytes (CD45/aSMA and CD45/NG2 cells) in the skin, but not in the heart, of AngII treated mice. MMP12KO mice infused with AngII showed markedly reduced expression of vascular injury markers and reduced number of PDGFRβ positive cells. Histological examination showed reduced perivascular collagen deposition in the heart and decreased collagen deposition in the skin of AngII treated MMP12KO mice. Moreover, total hydroxyproline content was reduced in the skin of MMP12KO mice infused with AngII.
Conclusions. These observations demonstrate that persistent injury to endothelial cells in AngII model may lead to activation of peri-endothelial cells resulting in fibrosis. Moreover, this study suggests that MMP12 is a key mediator of vascular injury and fibrosis in AngII model and may represent a therapeutic target in SSc.

PS31

RELATIONSHIP BETWEEN INTERLEUKIN-6 AND CARDIAC INVOLVEMENT IN SYSTEMIC SCLEROSIS

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Objectives. To explore the relationship between IL-6 levels and echocardiographic abnormalities, arrhythmia and heart rate variability, parameters of 6-minute walk test (6MWT), and NT-proBNP levels in SSc patients.
Methods. This case-control study included 31 SSc patients with preserved left ventricular ejection fraction (LVEF) and no concomitant disease, and 32 matched healthy controls.
All subjects underwent clinical examination, serological analysis, and echocardiographic assessment including pulsed-wave tissue Doppler imaging to evaluate cardiac function. They also underwent 24-hour Holter monitoring analysed for arrhythmia and heart rate variability (HRV) in the time domains, and 6MWT to evaluate exercise capacity.
Results. The level of IL-6 was significantly increased in patients with SSc (3.2 vs 2.2 pg/ml, p<0.001). SSc patients had significantly lower values of LV systolic (7.7 vs9.25 cm/s, p<0.001) and early diastolic (8.7 vs 10.3 cm/s, p=0.014) myocardial velocities and higher E/e' (9.04 vs 7.37, p=0.001) ratio, although there was no between-group difference according to LVEF (68 vs 65%, p=0.248). On evaluating right ventricle, there was no significant between-group difference in systolic tricuspid annular velocity (13 vs13.9 cm/s, p=0.105), but the peak early diastolic velocity was significantly lower (11.7 vs 13.6 cm/s, p=0.044) and E/e' significantly higher (4.3 vs 3.38, p=0.008) in SSc patients. Number of ventricular ectopic beats, prevalence of supraventricular tachycardia (SVT) episodes were increased in the patients with SSc compared to controls (p=0.046; p=0.027). In SSc patients, HRV analysis showed significantly lower values of SDNN (standard deviation of all NN intervals) (p=0.047). 6MWT distance was shorter in SSc as compared with healthy controls (p=0.004). IL-6 level showed correlation with LV mean e' (r=-0.57; p=0.001) and E/e' (r=0.55; p=0.001), aortic stenosis (r=0.49; p=0.003), prevalence of SVT(r=0.50; p=0.004), NT-proBNP (r=0.52; p=0.003), and disease activity according EUSTAR score (r=0.79; p<0.001).
Conclusion. Depressed cardiac function is common, even in asymptomatic patients with SSc. IL-6 level is increased in patients with SSc and significantly correlates with LV diastolic dysfunction, prevalence of aortic stenosis and supraventricular tachycardia episodes, NT-proBNP, and EUSTAR score. These results support the role of IL-6 in the development of cardiac disease in SSc patients.
Key words. systemic sclerosis, cardiac involvement, interleukin-6, tissue Doppler echocardiography, arrhythmia, heart rate variability, 6-minute walk test.

PS32

EXTENSION OF CARDIAC DAMAGE THROUGH THE DELAYED ENHANCEMENT OF CARDIAC MAGNETIC RESONANCE: PREDICTIVE VALUE OF A COMBINED APPROACH BASED ON CLINICAL AND LABORATORY FINDINGS, EKG-HOLTER AND CARDIAC MR

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Background. Cardiac involvement is a relevant prognostic determinant in Systemic Sclerosis(SSc), but the diagnosis is often delayed due to the lack of a specific diagnostic algorithm. Recently our group demonstrated the presence of histological myocarditis in patients with SSc and cardiac symptoms.
Methods. Forty SSc-patients with symptoms of cardiac involvement(dyspnea, palpitation) and/or signs of cardiac failure and elevation of cardiac enzymes underwent EKG-holter and cardiac magnetic resonance(CMR). Median follow-up was 24±0.2 months.
Results. Major EKG-holter modifications were present in 32.5% of patients. Twenty-two(55%) patients presented CMR-abnormalities. CMR study demonstrated T2 hyperintensity in 3 patients while none of the patients presented early gadolinium enhancement and 21(52.5%) patients presented late gadolinium enhancement(LGE). We identified 3 different patterns of distribution of LGE: subepicardial, midwall and subedocardial. Twelve patients presented a single pattern of distribution, while 7 patients(35.0%) presented more than one: 60.0% of patients presented a midwall distribution of LGE, 31.6% of patients presented a subepicardial LGE with a linear distribution pattern and 21.0% presented a subendocardial LGE distribution. Nineteen(47.5%) patients showed hypokinetic area and only one patient an akinetic area. The mean EF of left ventricle was 61.7±10.8%, and of right ventricle was 58.1±10.3%. Hypokinetic and akinetic area corresponded with the LGE area in all but one patient. 92.3% of patients with EKG-holter abnormalities showed CMR modifications suggestive of myocardial involvement, with respect to 37% of patients without EKG-holter abnormalities but with CMR modifications (p<0.001). Patients with major abnormalities on EKG-holter presented a higher number of involved myocardial segments on CMR (3.7±2.3) with respect to the patients without EKG-abnormalities (0.9±1.4) (p=0.012).
After a mean follow-up of 24±0.2 months, 4 patients(10%) died for arrhythmias or heart failure and 2 died for sepsis after a scleroderma renal crisis.
The 4 patients, who died at follow-up for cardiac complication, had severe dyspnea, elevated cardiac enzymes, myositis, major EKG-holter abnormalities, reduction of EF and LGE on CMR at baseline;75% of patients who died had a subendocardial distribution pattern of LGE on CMR.
Conclusions. These data confirm that SSc cardiac involvement is associated with a bad prognosis, expecially in patients with EKG-holter abnormalities and CMR modifications. The study of distribution of LGE and of hypo and akinetic areas on CMR is a useful tool to characterize the extension of myocardial damage, but probably only a combined approach, based on clinical presentation, laboratory parameters, EKG-holter examination and histological findings can identify patients with a poor outcome related to heart involvement in SSc.

PS33

KEY ROLE OF CARDIAC BIOMARKERS IN THE ASSESSMENT OF SYSTEMIC SCLEROSIS: CONTRIBUTION OF HIGH SENSITIVITY CARDIAC TROPONIN

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Objective. Microangiopathy is a cardinal feature of systemic sclerosis (SSc), which plays a critical role in the development of primary myocardial involvement and pulmonary hypertension, two major causes of death in SSc.
Our aim was to measure plasma concentrations of two cardiac biomarkers, high sensitive Cardiac troponin T (HS-cTnT), a marker of myocyte necrosis and/or ischemia, and N-terminal fragment of pro-BNP (NT-proBNP), a marker of cardiac strain, in two large cohorts of SSc patients and controls.
Methods. 161 SSc patients (aged 57±17 years, 135 women corresponding to 84%) were included and were compared to 213 healthy controls (aged 55±11, 170 women-80).
Results. Among the SSc cohort, mean disease duration was of 9±8 years, 65 patients (40%) had the diffuse cutaneous subset. HS-cTnT and NT-proBNP plasma levels were significantly increased in SSc patients versus controls (p=0.0001 and p<0.0001 respectively). SSc patients were more likely to have above the cut-off value concentrations of HS-cTnT (>14 ng/L) and NT-proBNP than controls (30/161 patients (19%) with HS-cTnT >14 ng/l vs. 4/213 controls (2%), p<0.0001; 17/161 patients (11%) with increased NT-proBNP levels vs. 8/213 controls (4%), p=0.02). Similar results were observed in the subgroup of patients free of any cardiovascular risk factors.
Associated factors with HS-cTnT levels >14 ng/L were diabetes mellitus (p=0.01), hypertension (p=0.04), pulmonary arterial hypertension (PAH) (p=0.02), diffuse cutaneous subset (p=0.03), ESR >28 mm (p=0.001) and previous treatment with prednisone (p=0.03). Logistic regression analysis confirmed diabetes mellitus, ESR >28 mm and the diffuse cutaneous subset as factors independently associated with HS-cTnT >14 ng/L.
Increased NT-proBNP concentrations were only associated with the presence of PAH (p=0.0001). The strength of the association between PAH and elevation of both HS-cTnT and NT-proBNP (p<0.0001) was more important than between PAH and NT-proBNP alone.
Conclusion. Plasma levels of HS-cTnT and NT-proBNP are increased in SSc patients. Associated factors with increased cardiac markers include the diffuse cutaneous subset and increased ESR, which are all markers disease activity. Given the prognostic significance of these biomarkers, they might be helpful to select the patients that justify further examinations in case of suspicion of cardiac complication.

PS34

THE ROLE OF INFLAMMATORY PROGENITORS IN MYOCARDIAL FIBROGENESIS IN THE INFLAMMATORY DILATED CARDIOMYOPATHY

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Background. Heart-specific inflammation– myocarditis is a common cause of pathological tissue remodelling and heart failure with the phenotype of inflammatory dilated cardiomyopathy (iDCM). During the last years there was a shift in SSc-related death causes, indicating iDCM as a major cause of death in these patients. Despite the high unmet clinical need, so far little is known about the etiology of iDCM and the mechanisms leading to heart dysfunction in SSc patients.
Objective. The mouse model of experimental autoimmune myocarditis (EAM) mimics human iDCM. We used this model to study mechanistic aspects of the progression from acute cardiac inflammation into iDCM.
Methods. Alpha-myosin heavy chain peptide/complete Freund's adjuvant immunization was used to induce EAM in wild-type and Nitric oxide synthase 2-deficient (Nos2-/-) BALB/c mice. Chimeric mice, reconstituted with enhanced green fluorescence protein (EGFP)+ bone marrow were used to track the fate of inflammatory cells. Inflammatory CD133+ progenitors were isolated from inflamed hearts, cultured *in vitro* and injected intracardially at different stages of EAM. In vitro inflammatory CD133+ progenitors were differentiated into myofibroblasts with TGF-β, and into macrophages with Macrophage-Colony Stimulating Factor (M-CSF).
Results. Myocarditis peaked 21 days after immunization and numbers of cardiac pathological myofibroblasts progressively increased on follow-up. In chimeric mice >60% of cardiac myofibroblasts were EGFP+ 46 days after immunization, indicating their bone marrow origin. At day 21 cardiac infiltrates contained about 30% of inflammatory CD133+ progenitors and only small subset expressed macrophage-specific antigen F4/80. CD133+, but not CD133- cells, isolated from acutely inflamed hearts represented the cellular source of cardiac myofibroblasts at late stage of EAM. Mechanistically, in vitro myofibroblast differentiation of inflammatory CD133+ progenitors depended on TGF-b-mediated phosphorylation of Smad proteins and activation of Wnt signalling. Anti-TGF-β antibody treatment prevented myocardial fibrosis in immunized mice, and inhibited myofibroblast differentiation of inflammatory CD133+ cells. CD133+/F4/80hi cells show impaired myofibrogenic potential compared to CD133+/F4/80- cells. M-CSF treatment of wild-type but not Nos2-/- mice with EAM markedly increased CD133+/F4/80hi cells in the myocardium, and CD133+ progenitors isolated

from M-CSF-treated wild-type mice failed to differentiate into myofibroblasts. Accordingly, M-CSF prevented post-inflammatory fibrosis and left ventricular dysfunction in wild-type but not in Nos2-/- mice.
Conclusions. Active and NOS2-dependent induction of macrophage lineage differentiation abrogates TGF-β-mediated myofibrogenic differentiation potential of heart-infiltrating inflammatory CD133+ progenitors. Thus, modulating the in vivo differentiation fate of specific progenitors might become a novel approach for the treatment of iDCM.

Poster Tour 6:
Outcomes, Quality of Life, Psychological & Social

PS35

AN INTERNATIONAL COLLABORATION TO CONDUCT LARGE-SCALE TRIALS OF NON-PHARMACOLOGICAL INTERVENTIONS IN SCLERODERMA: THE SCLERODERMA-PATIENT-CENTERED INTERVENTION NETWORK (SPIN)

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Background. Psychosocial and rehabilitation interventions are increasingly used to attenuate disability and improve health-related quality of life (HRQL) in chronic diseases, but are typically not available for patients with rare diseases such as scleroderma (systemic sclerosis, SSc). Conducting rigorous, adequately-powered trials of these interventions for patients with rare diseases is difficult, and there are no adequately powered RCTs published for any educational, psychological or rehabilitation interventions for people living with SSc. The Scleroderma Patient-centered Intervention Network (SPIN) is an international collaboration of patient organizations, clinicians, and researchers. The aim of SPIN is to develop a research infrastructure to test accessible, low-cost self-guided online interventions to reduce disability and improve HRQL for people living with scleroderma. Once tested, effective interventions will be made accessible through patient organizations partnering with SPIN.
Methods. SPIN utilizes a novel research design, the cohort multiple RCT (cmRCT) design to collect longitudinal data related to problems experienced by people living with SSc and as a framework for developing, evaluating, and delivering psychosocial and rehabilitation interventions. In the cmRCT design, patients consent to participate in a cohort for ongoing data collection. The aim is to recruit 1,500-2,000 patients from centers across the world within a period of 5 years (2013-2018). Currently, over 20 centers from Canada, US, France, UK, the Netherlands, Australia and Mexico are involved in the SPIN Cohort. Eligible participants are persons >=18 years of age with a diagnosis of systemic sclerosis. In addition to baseline medical data, participants will complete patient-reported outcome measures every 3 months. Upon enrolment in the cohort, patients will consent to be contacted in the future to participate in intervention research and to allow their data to be used for comparison purposes for interventions tested with other cohort participants. Once interventions are developed, patients from the cohort will be randomly selected and offered interventions as part of pragmatic RCTs. Outcomes from patients offered interventions will be compared to outcomes from trial-eligible patients who are not offered the interventions.
Discussion. The use of the cmRCT design, the development of self-guided online interventions, and partnerships with patient organizations will allow SPIN to develop, rigorously test, and effectively disseminate psychosocial and rehabilitation interventions for people with scleroderma on an ongoing basis.

PS36

EARLY MORTALITY IN AUSTRALIAN AND CANADIAN SCLERODERMA PATIENTS: RATIONALE FOR ESTABLISHING A MULTI-NATIONAL INCEPTION COHORT OF PATIENTS WITH SYSTEMIC SCLEROSIS

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Background and aim. Studies of 'prevalent' cohorts wherein most patients have longstanding disease at recruitment, may underestimate mortality in systemic sclerosis (SSc) due to survivor bias. The aim of this study was to quantify mortality in Australian and Canadian patients with SSc and to compare patients with prevalent and incident disease.
Methods. In each of the Australian and Canadian cohorts, we quantified mortality as 1) Standardised Mortality Ratio (SMR); 2) Years of Life Lost (YLL), based on Australian Bureau of Statistics and Statistics Canada data for the general population; and 3) Percentage survival in the first decade of disease in a) the whole 'prevalent' cohort and b) in a subset of patients recruited within 5 years of onset of the first non-Raynaud manifestation (the 'incident' cohort). We determined a single primary cause of death (SSc or non-SSc related) and all other SSc organ involvement that contributed to death, using a 'harmonised' death case report form.
Results. In the Australian cohort of 1279 patients, 55.7% of 97 deaths recorded between 2007 and 2012 were SSc related; the most common cause of SSc-related death was heart-lung disease (40/52 deaths; 24 PAH, 7 ILD, 9 PAH and ILD). Malignancy, atherosclerotic vascular disease and sepsis (21, 8 and 5/43 deaths, respectively) were the most common non-SSc related causes. Regardless of the primary cause, SSc organ involvement contributed to death in 60% of cases. In multivariable regression, predictors of mortality were male sex, older age at disease onset and presence of PAH. In the 'incident' Australian cohort of 333 patients, there were 24 deaths during follow-up, with PAH and ILD accounting for all early SSc-related deaths. In the prevalent (n=1308) and incident (n=338) Canadian cohorts, the findings were very similar, with 59.7% of 150 deaths in the prevalent cohort between 2005 and 2012 being SSc related; once again the most common cause of SSc-related death was heart-lung disease. As seen in Table I, SMR and YLL were higher, and % survival was lower in the incident cohorts compared with the respective prevalent cohorts.
Conclusion. Mortality in Canadian and Australian SSc patients is similar, and substantial. Our results suggest that prevalent cohorts underestimate mortality in SSc by failing to capture early deaths, particularly in diffuse disease. Collectively, these findings provide a compelling rationale for establishing a large multi-national inception cohort of patients with SSc to more accurately quantify early mortality in this disease.

Table I. A comparison of measures of mortality in Australian and Canadian 'prevalent' and 'incident' cohorts.

	Australian Patients 2007-2012		Canadian Patients 2005-2012	
	'Prevalent' cohort n=1279	'Incident' cohort n=333	'Prevalent' cohort n=1308	'Incident' cohort n=338
Number of deaths	97	24	150	53
SMR (95% CI)				
Women	6.4 (4.9-7.8)	5.7 (2.3-9.0)	4.1 (3.3-4.8)	5.3 (3.7-7.0)
Men	8.8 (5.1-12.6)	16.0 (7.3-24.7)	6.6 (4.4-8.9)	8.4 (3.9-13.0)
Overall	6.8 (5.6-7.9)	8.7 (5.6-11.8)	4.5 /3.9-5.1)	5.9 b(4.5-7.2)
YLL (years				
Women	15.9	18.1	19.3	20.7
Men	12.9	15.0	16.3	19.3
% survival in first decade of disease				
Diffuse disease	95%	70%	94%	70%
Limited disease	99%	95%	97%	85%

PS37

IMPACT OF AUTOANTIBODY PROFILE ON SURVIVAL IN SYSTEMIC SCLEROSIS

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Introduction. Although autoantibodies have been demonstrated to associate strongly with organ complications in systemic sclerosis (SSc), their association with survival remains unclear.
Methods. Autoantibody specificities were determined by the hospital Immunology laboratory in 649 consecutive SSc patients, followed for up to 15 years.
Results. The cohort had 84% female and 41% dcSSc patients. The most frequently observed antibody was anti-centromere antibody (ACA), found in 25.3% of the patients. Anti-topoisomerase I (ATA) was present in 23%, anti-RNA polymerase antibody (ARA) in 10.5% and anti-U3RNP in 4.6% of the aptients. More infrequently seen antibodies included anti-U1RNP in 5.9%, anti-PmScl in 3.7%, anti-Th/To in 0.6%, anti-Ku in 0.8%, anti-Jo1 in 0.9% and anti-Ro antibodies in 4.8%. Of the cohort, 3.4% were ANA negative and 3.4% had other rarer antibodies. Of the 118 (18.2%) patients who had unspecified anti-nuclear antibodies (ANA), 78% were tested for extractable nuclear antigen (ENA) reactivities and were negative. Of those, 66.4% had fine speckled, 27.4% had nucleolar and 35% had homogenous pattern.
Univariable Cox regression analysis revealed that the only SSc-specific antibody that demonstrated significant association with survival was ACA (HR 0.68, p=0.022). Nevertheless, when correcting for subset, the association disappeared, suggesting that the better survival among ACA positive patients is due to the predominantly limited skin involvement in this group.
On the other hand, unspecified ANA positivity significantly increased the risk of death (HR 1.89, p<0.001) and this was independent of subset. Analysis of each pattern separately demonstrated that this is mainly a results of the increased risk of death seen in patients with unspecified ANA with homogenous (HR 1.74, p=0.018) and fine speckled pattern (HR 1.47, p=0.049). KM survival at the end of follow-up was similar in patients with SSc-specific autoantibodies (67% in ARA, 59% in ACA, 55% in ATA and 53% in U3RNP positive patients) while demonstrating significant reduction in those with non-specified ANAs (34%).
We grouped together patients with unspecified ANAs and those with known antibody specificities, associated with the same pattern. Analysis of associations with disease outcome showed no difference in survival between patients with and without the three most frequently observed patterns.
Conclusions. While SSc-specific antibodies do not predict survival, unspecified ANAs may be associated with worse outcome. Pooling autoantibodies together showed no significant increase in mortality related to immunofluorescent pattern, which suggests that a potentially unidentified autoantibody may be associated with worse survival in SSc patients.

PS38

DEVELOPING AN INTERVENTION FOR BODY IMAGE DISTRESS IN SYSTEMIC SCLEROSIS: AN UPDATE FROM THE SCLERODERMA PATIENT-CENTERED INTERVENTION NETWORK (SPIN)

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Background. Appearance changes are common in systemic sclerosis. These changes often affect visible and socially relevant body parts, and can be difficult to conceal. Commonly affected parts of the body include face, mouth, and hands, and can include telangiectasias, calcinosis, hyper-/hypo-pigmentation of the skin, narrowing of the mouth and nose, digital ulcers, and hand contractures. Currently available medical treatments do little to ameliorate these changes. Research on systemic sclerosis has found that patients rate disease-related changes in appearance as one of the most significant stressors associated with scleroderma, and some patients experience significant body image distress. Body image concerns have been associated with depression, low self-esteem, anxiety, and social impairments, including problems in sexual functioning. However, to date there are no interventions available to address body image concerns in systemic sclerosis.
Objective. To develop and evaluate a web-based, patient-centered intervention designed to address body image distress in systemic sclerosis.
Methods. The Scleroderma Patient-centered Intervention Network (SPIN) is an international consortium of researchers, clinicians, patients, and patient advocates. The SPIN Body Image Distress Working Group brings together representatives from all of these groups to develop an online intervention for body image distress in systemic sclerosis. To date, the Working Group has reviewed the relevant research and clinical literature on body image distress in systemic sclerosis and has examined existing programs designed for other populations. Qualitative interviews have been conducted with patients and patient advocates in order to gain insights into body image concerns, and to obtain recommendations for program design and content.
Results. The online intervention addresses both personal and social aspects of body image concerns. Cognitive-Behavioral Therapy and Acceptance and Commitment Therapy approaches are incorporated. There is also an educational component that addresses body changes associated with scleroderma and how to cope with these changes across cognitive, emotional, and interpersonal levels.
Conclusion. This body image intervention for systemic sclerosis is a novel development that will fill a major gap in quality-of-life interventions available to patients with systemic sclerosis. The web-based design of the intervention makes it easily accessible to a wider range of patients than would otherwise have access to such a programme. A planned evaluation of the programme via a cohort multiple randomized controlled trial will be implemented to assess the intervention's efficacy.

PS39

IMPACT OF MALE SEX ON SURVIVAL IN SYSTEMIC SCLEROSIS

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Background/Purpose. Systemic sclerosis (SSc) has a female predominance with a female-to-male ratio of 3:1. Sex differences have been seen in many autoimmune diseases; however, little is understood about the effect of sex on SSc disease manifestations and survival. The objectives of this study were to evaluate differences in survival and disease manifestatons between males and females with SSc.
Methods. We conducted a retrospective cohort study of patients from the Toronto Scleroderma Program who fulfilled the American College of Rheumatology (ACR) classification criteria for SSc and were >16 years of age. We evaluated differences in age of onset, disease manifestations, serology, and survival between males and females.
Results. 907 patients (745 females, 162 males) were included. Males more frequently had diffuse SSc than women (45% versus 31%, p=0.007). Men were more likely to have renal crisis (10% versus 7%), abnormal nail fold capillaries (30% versus 25%), digital ulcers (35% versus 32%), esophageal dysmotility (89% versus 85%), telangiectasia (81% versus 77%), and interstitial lung disease (42% versus 32%). Females more frequently had anticentromere antibodies (19% versus 9%), pulmonary arterial hypertension (38% versus 33%), and Raynaud's phenomenon (96% versus 94%). There were 186 deaths (37 males, 149 females). Males had increased mortality compared to females (Hazard Ratio (HR) 1.56, p=0.02). The median survival time was 17.3 years for males and 24.7 years for females. After adjusting for differences in SSc subtype, serology and presence of interstitial lung disease, men still had increased mortality compared to females (HR 1.64, p=0.009).
Conclusion. Males with SSc have an increased burden of disease and decreased survival compared to females with SSc.

PS40

APPEARANCE DISSATISFACTION, SOCIAL DISCOMFORT, AND HELPLESSNESS IN PATIENTS WITH SYSTEMIC SCLEROSIS

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Background. Systemic sclerosis (SSc) has been related to marked appearance change (AC), particularly on the face, mouth, and hands. AC has previously been shown to have both personal (*i.e.*, body image) and interpersonal (*i.e.*, social relationships) components for patients with SSc. Because SSc-related disfigurement can be unpredictable and uncontrollable, AC may be associated with feelings of helplessness among patients with SSc.
Objective. The present study examined the relationship between satisfaction with appearance and helplessness in patients with SSc.
Methods. A sample of patients (N = 178) from the UCLA Quality of Life (QOL) Study completed the Brief Satisfaction With Appearance Scale (Brief-SWAP) and the Arthritis Helplessness Index (AHI, modified for scleroderma). The Brief-SWAP yields two subscales evaluating Dissatisfaction with Appearance and appearance-related Social Discomfort, in which higher scores indicate greater dissatisfaction or discomfort. The AHI yields two subscales of Helplessness (*e.g.*, My scleroderma is controlling my life) and Internality (*e.g.*, If I do all the right things, I can successfully manage my scleroderma), in which higher scores indicate greater helplessness/less control. In two separate models, hierarchical linear regressions examined the relationship of the Brief-SWAP subscales to each of the AHI subscales. Both models controlled for disease severity, as measured by the modified Rodnan skin score, and age. Age was considered in both models as a moderator of the relationship of Brief-SWAP subscales to AHI subscales.
Results. A significant main effect ($p<.001$) was found for appearance-related social discomfort as it relates to AHI Helplessness, such that greater social discomfort due to SSc-related AC was associated with greater feelings of helplessness. Dissatisfaction with appearance was not significantly ($p>.05$) associated with helplessness. In the model predicting AHI Internality, neither social discomfort nor subjective dissatisfaction with appearance demonstrated significant main effects ($ps>.05$) after controlling for disease severity and age. No significant interaction effects were found ($p>.05$).
Conclusions. These findings suggest that appearance-related social distress is associated with greater feelings of helplessness among SSc patients, while dissatisfaction with appearance is not. Although data analyzed here were cross-sectional, findings suggest that social challenges associated with scleroderma-related appearance changes may contribute to a sense of helplessness in patients. Given the extent of AC among SSc patients, this is an area that deserves greater study in order to increase understanding of the spectrum of outcomes associated with body disfigurement.

PS41

PREDICTION OF WORSENING OF SKIN FIBROSIS IN PATIENTS WITH DIFFUSE SYSTEMIC SCLEROSIS USING THE EULAR SCLERODERMA TRIALS AND RESEARCH (EUSTAR) REGISTRY AND VALIDATION IN A SECOND COHORT

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Objectives. To identify predictors for progressive skin fibrosis in patients with diffuse cutaneous SSc (dcSSc) to enable 1) clinical risk-stratification and 2) improved cohort enrichment in trials with skin fibrosis as the primary endpoint.
Methods. Observational prospective study using the EUSTAR database: Worsening of skin fibrosis was defined as increase in MRSS >5 points and >/=25% from the 1st to the 2nd visit. Inclusion criteria: dcSSc, ACR criteria fulfilled, MRSS>/=7 at 1st visit, valid data for MRSS at 2nd visit, period in between visits 12±2 months. In the univariate analysis, patients with progressive skin fibrosis were compared to non-progressive patients. Predictive markers with $p<0.2$ were included in the multivariate logistic regression analysis. For validation, a second cohort with new patients was extracted from the EUSTAR database 11 months after the first data extraction.
Results. Out of 637 patients, 9.7% had progressive skin disease. Patients with a lower MRSS (</=22/51) at baseline visit and shorter disease duration (</=15 months) developed significantly more often progressive skin fibrosis. Univariate analysis suggested the following prediction parameters: joint synovitis ($p=0.009$), disease duration ($p=0.023$), MRSS at baseline ($p=0.015$), and the interaction between disease duration and sex ($p=0.02$), respectively between disease duration and CK elevation ($p=0.047$).
In the multivariate analysis, different prediction models with varying combinations of the previously identified predictors were compared. The model with the highest prediction success rate (n=8/18, 44.4%) including joint synovitis, female sex, short disease duration, low MRSS at baseline, and the interaction of female sex and short disease duration, showed an area under the ROC curve of 0.73 (95% CI=0.66-0.79, $p<0.0001$) with an overall accuracy of 89.9% (98.1% for no progression, 14.3% for progression).
Other models with broader inclusion criteria revealed lower prediction success rates (e.g. 23.8% (n=20/84) for a model including low MRSS at baseline and short disease duration), but would simplify the recruiting process.
In the EUSTAR validation cohort, out of 188 patients, 6.4% had progressive skin disease. In the multivariate analysis, essentially the findings from the original cohort were confirmed. Interestingly, among the prediction markers, a low MRSS at baseline (</=22/51) had a particularly high impact in all prediction models (range OR 5.394–10.463).
Conclusion. These data from a large EUSTAR cohort analysis including a 2nd internal verification cohort demonstrated that the identified criteria allow the enrichment of clinical trials for dcSSc patients with progressive skin fibrosis by up to 4.5-fold which will have an important impact on the future clinical study design in SSc.

Poster Tour 7: *Imaging*

PS42

MRI INFLAMMATORY LESIONS OF THE HAND COULD BE PREDICTORS OF DIGITAL ULCERS, DISEASE ACTIVITY AND LOWER FUNCTIONAL CAPACITY IN SYSTEMIC SCLEROSIS

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Background. Joint involvement is frequent finding and correlate with poor life quality in systemic sclerosis (SSc). MRI is useful method for detecting and quantification of inflammatory lesions of the hand (bone oedema, erosions, synovitis and tenosynovitis) in systemic sclerosis patients.
Objective. The aim of the study was to investigate association of clinical features, laboratory tests and probability for the occurrence of inflammatory changes on the hand in systemic sclerosis.
Method. 102 patients with systemic sclerosis were investigated (mean age 53y). Contrast enhanced, low field MRI of the wrist and MCP2-5 joints was performed to all the patients. MRI inflammatory changes (bone oedema, erosions , synovitis and tenosynovitis) were assessed and scored by OMERACT RAMRIS scoring system. Different clinical features (age, sex, SSc subtype, disease duration (date of first non Raynaud symptom), Raynaud phenomenon, articular or periarticular pain, joint swelling and contractures, digital ulceration, HAQ, acroosteolysis (by standard PA radiographs of hand and wrist), pulmonary fibrosis (by CT and pulmonary function tests), pulmonary arterial hypertension (pulmonary arterial pressure higher than 30mmHg at rest on Doppler echocardiography) and laboratory tests (antinuclear antibodies, anti topoisomerase antibodies, anti centromere antibodies, RF, CRP,Creatine phosphokinase) and disease activity (by Valentini index) were carried out.
Results. By multiple logistic regression analysis taking into account all clinical and laboratory variable, we found that MRI inflammatory lesions of the hand were associated and probability for the occurrence of inflammatory changes was higher for the SSc patients with digital ulcers (OR=4.687;95%IP: 1,002-22,256; $p<0,05$), HAQ>1,5 (OR=8,226;95%IP: 1,740-38,896; $p<0,01$) and disease activity (OR=3,132; 95%IP: 1,027-9,551; $p<0,05$).
Conclusion. Inflammatory findings (bone oedema, erosions, synovitis ant tenosynovitis) on the hand by MRI in SSc could be predictors for digital ulcers, active disease and impaired functional capacity in systemic sclerosis .Regular monitoring of clinical features and organ involvement are essential in all the patients with systemic sclerosis, especially those with proven inflammatory changes on MRI of the hand.

Characteristics	CML	95% CI for CMC		p
Age	1.024	0.962	1.069	0.271
Disease duration	1.061	0.963	1.168	0.233
Female	0.953	0.100	9.128	0.967
Disease duration >5 y	1.143	0.372	3.511	0.816
Diffuse SSc	0.745	0.215	2.578	0.642
Raynaud phenomenon	0.000	0.000	–	0.999
Digital ulcers	4.687	1.002	22.256	0.049
HAQ < 1.5	0.236	1.740	38.896	0.008
Distal Phalange reception	3.488	0.727	16.732	0.118
Muscle ??????	1.049	0.110	10.048	0.967
DLCO <??	1.971	0.366	0.167	0.286
FVC <75%	1.130	0.277	4.416	0.864
?PAP>30mmHg	5.224	0.641	42.561	0.122
Positive ANA	1.099	0.309	3.904	0.884
Creatine phosphokinase	-	0.000	-	0.999
Positive CRP	2.656	0.549	12.841	0.224
Positive RF	-	0.000	-	0.999
Active disease	3.132	1.027	9.551	0.045

PS43

EVALUATION OF BLOOD PERFUSION IN DIFFERENT SKIN AREAS OF SYSTEMIC SCLEROSIS PATIENTS BY LASER SPECKLE CONTRAST ANALYSIS AND CORRELATIONS WITH NAILFOLDMICROANGIOPATHY EXTENT

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Objective. This study aimed at investigating by laser speckle contrast analysis (LASCA) blood perfusion (BP) at different skin sites in systemic sclerosis (SSc) patients, looking for any correlation with the extent of the nailfold capillary damage.
Methods. Sixty-eight SSc patients (mean disease duration 7±6 years) and 68 healthy subjects (CNT) matched for age and sex were enrolled. BP was assessed by LASCA in the facial and dorsal/palmar regions of the hand in both SSc patients and CNT. Different regions of interest (ROI) were created on their hands: fingertips, periungual areas, dorsum and palm of both hands as well as their face: forehead, tip of nose, zygomas and perioral regions. The average BP was scored as perfusion units (PU) (1). Videocapillaroscopy (NVC) was used to detect the proper pattern of nailfold microangiopathy (early, active or late) (2).
Results. SSc patients had a statistically significant lower median BP than CNT at the level of fingertip (86 and 189 PU, respectively, $p<0.0001$), periungual (69 and 140 PU, respectively, p<0.0001) and palm areas (78 and 111 PU, respectively, $p<0.0001$). Whereas, both groups had similar BP values at dorsum of hands, whole face, and different ROIs of the face. There was a statistically significant correlation between BP of the fingertips and BP of the periungual areas in both SSc patients and CNT ($p<0.0001$). A statistically significant correlation was also observed in both groups between palm and fingertip areas ($p<0.0001$), dorsum and periungual areas ($p=0.0003$ and p=0.05, respectively), dorsum and palm ($p=0.0008$ and p=0.0001, respectively). The median BP gradient between fingertips and palm was lower in SSc patients than in CNT (11 and 67 PU, respectively, $p<0.0001$), as was the gradient between the dorsum and periungual areas (25 and 69 PU, respectively, $p=0.0009$). A significant progressive decrease of BP was observed in SSc patients with progressive pattern of nailfold microangiopathy (early, active, and late) at the level of fingertip (p=0.004), periungual ($p=0.007$) and palm areas ($p=0.02$).
Conclusions. This study shows that LASCA detects significant differences in BP at the level of fingertips, periungual areas, and palm of hands in SSc patients versus CNT. Furthermore a statistically significant correlation was observed between nailfold microangiopathy extent and BP at the level of fingertips, periungual areas, and palm of hands in SSc patients.
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PS44

CORRELATION BETWEEN BLOOD PERFUSION AND DERMAL THICKNESS IN DIFFERENT SKIN AREAS OF SYSTEMIC SCLEROSIS PATIENTS.

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Objective. The aim of this study was to identify possible correlations between peripheral blood perfusion (BP) and dermal thickness (DT) in three different areas of skin (periungual, dorsum of hand and zygoma), in SSc patients.
Methods. Sixty-three SSc patients (mean age 64±11SD years) were enrolled. BP was analysed by laser speckle contrast analysis (LASCA) at the level of dorsal region of hands and face in SSc patients (1). Different regions of interest (ROI) were created at level of periungual areas of the 3rd finger bilaterally, dorsum of both hands and zygomas, and the average BP was scored as perfusion units (PU). Both high frequency ultrasound (US) and modified Rodnan skin score (mRss) were used to evaluate average DT at the level of dorsum of 3rd finger, hand and zygoma bilaterally (2). US and LASCA were also performed in 63 age and sex matched healthy subjects (CNT).
Results. A negative correlation was observed between BP and both ultrasound-DT ($p=0.0005$) and mRss ($p=0.007$) in SSc patients at the level of fingers. No statistically significant correlation was found between BP and both ultrasound-DT and mRss at level of dorsum of hand and zygomas in SSc patients. In CNT no statistically significant correlation was detected between BP and ultrasound-DT at the level of fingers, dorsum of hands or zygomas. SSc patients showed a statistically significant lower BP at level of periungual areas when compared with healthy subjects ($p<0.0001$). No statistically significant difference in BP values was observed between SSc and CNT at the level of dorsum of hand and zygomas. SSc patients showed a statistically significant higher ultrasound-DT at the level of periungual areas, dorsum of hands and zygomas than CNT ($p<0.0001$, for all). A statistically significant positive correlation was observed between ultrasound-DT and mRss in SSc patients at level of the three areas (periungual $p<0.0001$; dorsum of hand $p=0.03$; zygoma $p=0.0001$).
Conclusions. This study demonstrates a relationship between periungual BP evaluated by LASCA and finger DT evaluated by both US and mRss in SSc patients. SSc patients have a statistically significant higher DT at level of dorsum of finger, hand or zygoma than healthy subjects. There is a significant positive correlation between US and mRss in the assessment of DT.
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PS45

STABILISATION OF MICROCIRCULATION IN EARLY SYSTEMIC SCLEROSIS PATIENTS WITH DIFFUSE SKIN INVOLVEMENT FOLLOWING RITUXIMAB TREATMENT

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Background. Systemic sclerosis (SSc) is a multisystemic autoimmune disease characterized by fibrosis of the skin and internal organs, generalized microvasculopathy and antibody response against various cellular antigens. In between others, our group recently reported stabilisation of internal organ involvement during 2-year follow-up in an open pilot study of a 2-treatment course (month 0/6) of rituximab (RTX) in patients with early diffuse SSc (dcSSc). As SSc is characterized by progressive microangiopathy over time it may be worthwhile to investigate whether treatment with RTX could also stabilize microangiopathy in dcSSc.
Aim. This study assesses microangiopathic evolution by nailfold videocapillaroscopic (NVC) analysis after two treatment course (month 0/6) with rituximab in early dcSSc patients.
Methods. Twelve months follow-up (open-label study) of six consecutive patients with early dcSSc. Patients received an infusion of two times 1000 mg RTX at month 0 and 6, together with 100 mg methylprednisolone. Low-dose prednisolone (no higher than 10 mg/day) was allowed, provided that patients were

taking a stable dose at least 12 weeks before inclusion. All disease-modifying antirheumatic drugs (except methotrexate) were stopped 12 weeks before screening. Patients were on a stable dose methotrexate (10-25 mg/week) as background therapy since at least 12 weeks. Capillaroscopic assessment, clinical read outs (modified Rodnan skin score, mRSS; lung function and echocardiography) and disease activity score (DAS) were performed at 0, 3, 6 and 12 months.

Results. There was a clinical significant change in skin score with a mean (SD) mRSS of 24.8 (5.95) at baseline and 10.2 (1.17) at month 12 (Mixed Model Analyses, MMA, $p<0.001$) and a significant decrease in DAS, with a mean of 4.2 (1.69) at baseline and 0.6 (0.74) at month 12 (MMA $p<0.001$). Indices of internal organ involvement remained stable (Table I). Semi-quantitatively scored NVC parameters remained stable showing no progression of the microvascular damage during follow-up: mean score (SD) of capillary loss at baseline/12 months: 2.170 (0.408)/ 1.830 (0.408) (MMA $p=0.341$), mean score (SD) of giants at baseline/ 12 months: 0.670 (0.516)/ 1.17 (0.408) (MMA $p=0.093$), mean score of haemorrhages at baseline/12 months: 0.670 (0.516)/1.00 (0.000) (MMA $p=0.529$) and mean score of neoangiogenesis at baseline/12 months: 0.830 (0.408)/ 0.830 (0.753) (MMA $p=0.383$) (Table II).

Conclusions. This is the first open pilot study to show that two immunosuppressive treatment courses with RTX may not only have potential efficacy for skin and stabilisation of internal organ involvement but also additional stabilisation of microangiopathic parameters in early dcSSc.

Table I. Changes in clinical parameters in patients with early and severe Diffuse cutaneous Systemic Sclerosis (DcSSc) treated with Rituximab (n=6).

Variable	Statistic	0M	3M¶	*p*-value*	6M	*p*-value*	12M	*p*-value* MMA 12M	*p*-value
mRSS	Mean, SD Median (QLQ3) Min, max	24.8 (5.95) 25.0 (19.3, 30.0) (17.0, 33.0)	18.6 (8.68) 15.0 (12.5, 26.5) (11.0, 33.0)	0.026	13.8 (5.19) 13.5 (8.8, 19.3) (8.9, 20.0	<0.001	10.2 (1.17) 10.0 (9.0, 11.3) (9.0, 12.0)	<0.001	<0.001
DLCO (% of normal)	Mean, SD Median (Q1, Q3) Min, max	70.2 (12.98) 68.0 (59.8, 85.0) (53.0, 85.0)	61.0 (12.21) 61.0 (51.0, 71.0) (44.0, 78.0)	0.105	66.5 (15.98) 67.0 (57.5, 5,3) (41.0, 91.0)	0.213	69.3 (18.13) 69.5 (59.0, 83.8) 38.0, 92.0)	0.771	0.302
FVC (% of normal)	Mean, SD Median (Q1, Q3) Min, max	99.7 (13.77) 99.0 (88.8, 113.3) (79.0, 117.0)	94.4 (11.08) 97.0 (84.0, 103.5) (77.0, 105.0	0.590	100.5 (17.74) 100.5 (86.0, 116.0) (74.0, 125.0)	0.808	101.2 (13.85) 105.5 (91.0, 111.5) (76, 113)	0.646	0.781
TLC (% of normal)	Mean, SD Median (Q1, Q3) Min, max	87.5 (9-40) 87.0 (78.0, 94.8) (78.9, 103.0)	83.8 (9.52) 81.0 (76.5, 92.5) (74.0, 99.0)	0.970	88.7 (1574) 85.0 (78.3, 103.8) (68.0, 112.0)	0.740	94.5 (14.6) 94.0 (83.8, 104.5) (74.0, 118.0)	0.062	0.191
FEV (% of normal)	Mean, SD Median (Q1, Q3) Min, max	92.5 (10.15) 90.0 (83.5, 104.3) (82.0, 105.0	91.0 (12.02) 95.0 (78.5, 101.5) (77.0, 105.0	0.447	91.8 (12.29) 95.0 (79.3, 101.0) (74.0, 107.0)	0.796	97.3 (11.76) 98.0 (87.5, 107.0) (80, 113)	0.077	0.088
DAS	Mean, SD Median (Q1, Q3) Min, max	4.2 (1.69) 3.8 (3.1, 5.5) (2.0, 7.0)	1.8 (1.15) 2.0 (0.75, 2.75) (0.0, 3.0)	<0.001	1.1 (0.58) 1.0 (0.5, 1.6) (0.5, 2.0)	<0.001	0.6 (0.74) 0.5 (0.0, 0.88) (0.0, 2.0)	<0.001	<0.001
sPAP /mmHg)	Mean, SD Median (Q1, Q3) Min, max	30.5 (2.65)* 31.0 (27.8, 32.8)¶ (27.0, 33.0) ¶	30.4 (6.19) 28.0 (25.5, 36.5) (23.0, 39.0)	0.581	33.0 (8.25)¶ 32.0 (25.5, 41.0) ¶ (23.0, 44.0)¶	0.734	30.4 (4.45)¶ 0.430 29.0 (26.5, 35.0)¶ (25.0, 35.0)¶	0.603	
LVEF (% of normal)	Mean, SD Median (Q1, Q3) Min, max	58.5 (8.10)* 57.5 (51.3, 66.8)* (50.0, 69.0)	65.8 (7.82) 69.0 (58.0,72.0) (55.0, 75.0)	0.094	59.5 (4.93) 59.0 (55.0, 63.3) (55.0, 67.0)	0.830	63.5 (5.72) 64.0 (58.8, 69.0) (55.0, 69.0)	0.239	0.238

*Significance of all values versus baseline; aN=5. *N=4, MMA: Mixed Model Analysis; mRSS: modified Rodman skin score; DLCO: diffusion capacity for carbon monocide; FVC: forced vital capacity; TLC: total lung capacity; FEV: forced expiratory volume; DAS: disease activity score; sPAP: systolic pulmonary artery pressure; LVEF: left ventricular ejection fraction.

Table II. Microangiopathic evolution (semi-quantitative scores) in patients with early bDcSSc treated with rituximab (N=6).

Cap Variable	Statistic	0M	3M¶	*p*-value*	6M	*p*-value*	12M	*p*-value*	*p*-value MMA
SQ Capillary loss	Mean, SD Median Min, max	2.17 (0.408) 2.0 (2.0, 2.25) 2.0, 3.0	2.20 (0.447) 2.0 (2.0, 2.50) 2.0, 3.0	0.915	2.17 (0.753) 2.0 (1.75, 3.00) 1.0, 3.0	1.000	1.83 (0.408) 2.0 (1.75, 2.00) 1.0, 2.0	0.147	0.341
SQ Giants	Mean, SD Median Min, max	0.67 (0.516) 1.00 (0.00, 1.00) 0.00, 1.00	1.00 (0.000) 1.00 (0.00,1.00) 1.00, 1.00	0.122	1.00 (0.000) 1.00 (0.00, 1.00) 1.00, 1.00	0.099	1.17 (0.408) 1.00, 1.25 1.00, 2.00	0.016	0.093
SQ Haemorrages	Mean, SD Median Min, max	0.67 (0.516) 1.00 (0.00, 1.00) 0.00, 1.00	0.80 (0.447) 1.00 (0.50, 1.00 0.00, 1.00	0.590	0.83 (0.408) 1.00 (0.75, 1.00 0.00, 1.00	0.463	1.00 (0.000) 1.00 (0.00, 1.00 1.00 1.00	0.154	0.529
SQ Neoangiogenesis	Mean, SD Median Min, max	0.83 (0.408) 1.00 (0.75, 1.00) 0.00, 1.00	1.20 (1.095) 1.00 (0.50, 2.00) 0.00, 3.00	0.132	1.00 (0.632) 1.00 (0.75, 1.25) 0.00, 2.00	0.573	0.83 (0.753) 1.00 (0.00, 1.25 0.00, 2.00	1.000	0.383

**p*-value versus Baseline; SQ: semi-quatitative; ¶N=5.

PS46

ASSESSMENT OF SKIN BLOOD FLOW AND STRUCTURE IN LOCALISED SCLERODERMA USING NON-INVASIVE IMAGING

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Background. Localised scleroderma (morphoea) often occurs in patients with no other symptoms of a connective tissue diease such as systemic sclerosis (SSc). Extensive morphoea can cause major morbidity, disability and disfigurement and its pathophysiology is poorly understood. Studying morphoea enhances knowedge of the structure and function of areas of skin affected by scleroderma, isolated as they are from the other disease processes associated with SSc; this consequently enables a better understanding of the pathogenesis of scleroderma in general. The aim of this study was to investigate, with non-invasive imaging, the relationship between perfusion and the localised abnormalities of skin structure which characterise morphoea.
Methods. 32 patients with morphoea underwent imaging at affected and unaffected sites. The skin was imaged with high frequency ultrasound (HFUS) and optical coherence tomography (OCT) to determine thickness. Perfusion was imaged directly with dual wavelength (red [deeper] and green [superficial]) laser Doppler imaging (LDI), and indirectly with thermography.
Results. Epidermal and dermal thickness was decreased at affected compared to unaffected sites; however, only differences in epidermal thickness (p=0.03 [HFUS] and p=0.005 [OCT]) were significant for active plaques, and only one of the epidermal thickness measurements (p=0.11 [HFUS] and p=0.004 [OCT]) was significant for inactive plaques. Deeper perfusion was higher within plaques than at unaffected sites (p<0.001 for red LDI, p<0.0001 for thermography) but superficial perfusion (green LDI) was similar between sites. An inverse association was found between epidermal thickness and superficial perfusion (HFUS and green LDI) but no association was found for deeper perfusion (HFUS and thermography).
Conclusions. This is the first study of morphoea to look for associations between HFUS, OCT and LDI and thermography. The study confirms loss of epidermal thickness and an increase in deeper perfusion in morphea plaques. Changes in soft tissue thickness are not confined to epidermis and dermis but occur also in underlying tissue (evidenced by red LDI results). The relationship between perfusion and the loss of subcutaneous tissue requires further investigation to fully understand the pathogenesis of morphea plaques.

PS47

VIRTUAL TOUCH IMAGING AND QUANTIFICATIONTM: IS IT POSSIBLE TO DISTINGUISH "UNAFFECTED" SKIN IN PATIENTS FROM HEALTHY SKIN?

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Background/Purpose. Skin involvement is a fundamental clinical feature in systemic sclerosis (SSc), often considered the primary outcome in clinical trials. Nonetheless, it remains orphan of a sensitive and reliable quantitative assessment technique. Virtual Touch Imaging and Quantification (VTIQ) is a new elastography imaging method that provides qualitative and quantitative information about absolute skin stiffness.
The purpose of this study was to compare absolute skin stiffness values of clinically unaffected scleroderma skin and the skin of healthy controls (HC), using VTIQ.
Method. Absolute skin stiffness was measured on the basis of shear-wave velocity (expressed in meters per second), using a VTIQ, at 16 of the 17 anatomical sites of the modified Rodnan skin score (mRSS) (anterior chest, abdomen, upperarms, forearms, fingers, hands, thighs, legs and feet bilaterally). Twenty-six patients (13 limited SSc, 13 diffuse SSc), and 17 age- and gender-matched HC were included.
Higher shear-wave velocity values represent harder tissues. mRSS was established at each anatomical site by an assessor blinded to the VTIQ findings. For the purpose of this study we only included, for SSc patients, anatomical sites with clinically unaffected skin (local mRSS = 0). Comparison between groups was performed through Mann-Whitney test, p values <0.05 were considered significant.
Results Absolute skin stiffness measurements were higher in all SSc "unaffected" areas than in the HC, reaching statistical significance in eight out of 16 measurements sites (See Table I).
Conclusion. VTIQ adds sensitivity to the assessment of skin stiffness in SSc. What appears to be "normal" skin in SSc may be already pathologic, as shown by increased sheer-wave velocity. VTIQ may help in the identification of patients in an early phase of the disease and assist in the evaluation of novel therapies.

Table I. Shear wawe velocities values (m/s) in SSc patients and controls.

	Patients	n (*)	Controls	Differences between patients and conrols (p values)
Anterior chest	2.8 (0.7)	17*	2.3 (0.7)	0.05
Abdomen	2.5 (0.4)	21	2.0 (0.6)	0.016
Upperarm left	2.7 (0.5)	19	2.3 (0.4)	0.004
Upperarm right	2.4 (0.4)	18	2.2 (0.5)	NS
Forearm left	2.5 (0.3)	14	2.1 (0.4)	0.008
Forearm right	2.5 (0.4)	13	2.3 (0.3)	NS
Hand left	2.6 (0.4)	7	2.2 (0.5)	NS
Hand right	2.7 (0.4)	7	2.2 (1.1)	0.011
Phalanx left	2.7 (0.4)	1	2.3 (0.4)	-
Phalanx right	3.1 (0.8)	3	2.2 (0.4)	-
Thigh left	2.3 (0.6)	23	2.1 (0.3)	NS
Thigh right	2.4 (0.4)	23	2.1 (0.2)	0.004
Leg left	3.1 (1.0)	19	2.4 (0.4)	0.012
Leg right	2.6 (0.5)	18	2.5 (0.5)	NS
Foot right	2.9 (0.7)	14	2.2 (0.3)	0.003
Foot left	2.6 (0.6)	15	2.3 (0.4)	NS

Shear wawe velocities values (m/s) are shown as mean (standard deviation). p<0.06 was considered statistically significant. NS: not significant; n (*) Number of sites from 26 SSc patients with local mRSS = 0. Of the patients with mRSS=0, 18 had a limited SSc, and one had a diffuse SSc.

PS48

IMAGING OF SCLERODERMA WITH OPTICAL COHERENCE TOMOGRAPHY

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Background. Systemic scleroderma (SSc) is a connective tissue disease with abnormalities in vascular, immunological and fibrotic pathways. The vasculopathy is characterized by fibrointimal proliferation of small vessels and vasospastic episodes that may lead to tissue ischaemia and over time morphological skin changes characterized by skin fibrosis. Optical Coherence Tomography (OCT) provides a non-invasive, easily applicable optical imaging method for assessment of skin. In several clinical studies using OCT scanning, it has been demonstrated a potential tool for non-invasive assessment of non-melanoma skin cancer. Scleroderma is characteristic in OCT scans due to the homogeneous appearance of dermis due to fibrosis. This poster demonstrates the characteristic OCT morphology of scleroderma and other skin conditions with fibrosis.
Methods. Skin morphology and scar formation were studied using VivoSight OCT scanner (Michelson Diagnostics Ltd., UK). The system's 10 micron axial resolution is complemented by 7.5 micron lateral resolution throughout a 2 mm depth range in tissue. OCT is an optical analogue of ultrasound imaging, the images produced are similar to b-mode ultrasound images, showing a vertical section of the tissue but with a resolution better than a typical high-frequency ultrasound system.
Results. The normal skin in OCT scans clearly demonstrates the well-known layering of the skin. This architectural pattern is, however, in striking contrast to the OCT images obtained from scleroderma skin and other similar skin conditions as keloids. In scleroderma a disarray of the normal layering of the skin was demonstrated. The OCT images displayed no difference between the two types of scleroderma (morphea and systemic scleroderma). However, in contrast to keloid

tissue the scleroderma images displayed a more cohesive appearance indicating a difference in density of collagen or other dermal structures. The poster will display multiple OCT images.
Conclusion. In scleroderma novel anti-fibrosing agents and other treatment options are emerging and non-invasive monitoring of dermal collagen morphology is warranted during treatment trials. An OCT study from 2013 has demonstrated a good correlation between OCT images of systemic scleroderma skin and the modified Rodnan skin score and further OCT studies of scleroderma is ongoing.

Poster Tour 8: *Therapy / Miscellaneous*

PS49

TOWARDS PERSONALIZED MEDICINE: MOLECULAR DIAGNOSTICS FOR SYSTEMIC SCLEROSIS – UTILIZING GENE EXPRESSION PROFILING TO GUIDE PATIENT MANAGEMENT

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Systemic sclerosis (SSc) is a devastating autoimmune disease of unidentified etiology. To date, almost every efficacy trial in SSc has failed. However, multiple SSc clinical trials have shown efficacy for subsets of patients for unknown reasons. Gene expression analysis has elucidated a fundamental factor underlying these challenges: SSc is a heterogeneous disease and the molecular pathways underlying the disease differ among subsets of patients. Clinically similar patients, all diagnosed with SSc, may have different deregulated pathways underlying their particular disease. While cutaneous fibrosis, internal organ involvement, vascular abnormalities and autoantibody formation are common across subtypes, prognosis and response to therapy vary with gene expression subtypes. This is critical to both the treatment of individual patients and the clinical development of novel therapies.
Gene expression profiling and molecular classification of SSc patients can reveal actionable molecular information to inform treatment decisions. This approach is now standard for other diseases, e.g. stratification of breast cancer patients, 25-30% of whom overexpress HER2, which drives tumor growth. Administering Herceptin, which targets HER2, to a global population of breast cancer patients would be detrimental (due to side effects), ineffective (due to non-responders), and uneconomical. But the ability to molecularly classify patients has rapidly transformed care for this and other disease states.
We have developed a microarray-based test (ScleroType™) that distinguishes the natural subtypes of SSc. Knowledge of the pathological factors that drive disease enables the precise selection of drugs that specifically target the patient's deregulated pathway, and the precise selection of patients that are able to respond to a specific drug under development while delivering real-time quantitative feedback as to whether a drug is working in that patient. In an investigator-initiated clinical trial of mycophenolate mofetil (MMF), nearly all SSc patients who demonstrated clinical improvement (assessed by skin score) belong to the inflammatory gene expression subset. In contrast, in trials for imatinib mesylate, patients who demonstrated improvement expressed a fibroproliferative gene expression signature. Work with other established and experimental drugs is ongoing.
Celdara Medical provides detailed molecular profiling for SSc as a service, in a highly automated and controlled CLIA-certified environment. We are receiving reimbursement for this test from leading American insurance companies. Physicians, drug developers, and of course, patients will benefit from the fundamental knowledge about a specific patient's disease that is provided by molecular subtyping. Here we present the state of the art as well as future directions being undertaken in our labs.

PS50

ANTI IL-6 RECEPTOR ANTAGONIST FOR THE TREATMENT OF DIFFUSE CUTANEOUS SYSTEMIC SCLEROSIS

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Background. Systemic sclerosis (SSc) is an autoimmune connective tissue disorder of unknown etiology that is characterized by fibrosis of the skin and internal organs. Few reports have hypothesized that interleukin-6 (IL-6) is involved in the pathogenesis of SSc. Tocilizumab is an IL-6 receptor antagonist used primarily for the treatment of rheumatoid arthritis. Currently there is growing evidence for the benefit of Tocilizumab in other systemic autoimmune diseases, including SSc.
Objective. To examine the effects of Tocilizumab treatment on patients with severe diffuse cutaneous SSc (dcSSc) in whom conventional treatments for SSc have failed.
Methods. Three dcSSc patients were administered Tocilizumab at a dose of 8 mg/kg body weight once every 4 weeks. All patients had severe dcSSc with cutaneous and systemic involvement, and an immense negative impact on their quality of life. Clinical and biological assessments were performed before and after 4 to 14 infusions of Tocilizumab.
Results. All three patients showed disease improvement with Tocilizumab treatment. Patients' blood works normalized or improved substantially. Rodnan skin score and swollen and tender joint counts decreased. The two patients who suffered from lung involvement showed improved respiratory function tests. All three patients had improved ADL (activities of daily living) scores with Tocilizumab treatment. However, Tocilizumab treatment had no effect on the patients' Raynaud's phenomenon, digital ulcers or gastro-intestinal reflux. Tocilizumab was well tolerated by all three patients.
Conclusion. All three cases of dcSSc reported showed improvement under treatment with Tocilizumab. Tocilizumab may be beneficial for the treatment of resistant SSc. Tocilizumab should be considered as treatment in cases of sever SSc where conventional treatment has failed, or alternatively for patients with contraindications for conventional treatment.

PS51

SAFETY AND EFFICACY OF COMBINED B CELL-DEPLETION THERAPY WITH RITUXIMAB AND CYCLOPHOSPHAMIDE IN SYSTEMIC SCLEROSIS.

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Introduction. Systemic sclerosis (SSc) is a multisystemic autoimmune disease characterized by fibrosis of skin and internal organs, generalized microvasculopathy, and antibody response against various cellular antigens. There is growing evidence that B cells play a key role in the pathogenesis of Systemic Sclerosis (SSc)1. Cyclophosphamide is the most widely used and studied treatment for early and severe SSc-ILD2. Furthermore there are preliminary studies on the efficacy of Rituximab in SSc skin involvement3. However there are no data about combined B cell-depletion therapy with Rituximab and Cyclophosphamide.
Objective. Clinical assessment of combined B cell-depletion therapy with Rituximab and Cyclophoshamide in SSc.
Materials and Methods. Patient 1: 48-year-old women, affected by lcSSc with rapidly progressive skin involvement, polyarthritis and mild lung involvement; anti-Scl70 negative, anti-RP11 positive; basal Modified Rodnan Skin score 17. Patient 2: 44-year-old man, with recent onset lcSSc characterized by severe rapidly progressive skin involvement, oesophageal and joint involvement; anti-Scl70 negative, anti-RP11 positive; basal Modified Rodnan Skin score 27.
Both patients received Rituximab 1 gm on days 1 and 15 plus Cyclophosphamide 500 mg every two weeks for six months. Patients were retreated after nine months with Rituximab (1 gm x 2). Patients were evaluated every three months, with total follow-up of 12 months.
Results. Both patients showed a decrease in Modified Rodnan Skin score. In patient 1, who presented a less severe cutaneous involvement, skin involvement improved dramatically. In both patients there was an improvement of joint involvement; patient 1 doesn't need DMARDS therapy while patient 2 started Methotrexate three months after retreatment with Rituximab. There was also an improvement of quality of life evaluated by SF-36 Questionnaire, in particular in the items concerning physical functioning, role-physical and bodily pain. The

combined therapy Rituximab plus Cyclophosphamide was well tolerated; no patient showed neutropenia. Patient 2 presented cutaneous herpes zoster reactivation 8 months after the beginning of the protocol.

Conclusions. Combined B cell-depletion therapy with Rituximab and Cyclophosphamide in SSc represents an effective and acceptable choice in selected patients with progressive SSc.

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Table.

	Pt. 1			Pt.2		
	0	+6M	+12 M	0	+6 M	+12 M
Tender J	4	0	0	7	0	2
MRSS	17	15	7	27	21	20
SF 36 FP	10	-	65	10	-	45
SF 36 RP	0	-	50	0	-	25
SF 36 BP	30	-	84	0	-	30
SF 36 GH	20	-	37	10	-	35
SF 36 VT	15	-	50	10	-	15
SF 36 SF	37	-	75	25	-	12
SF 36 RE		100	-	0	-	33
SF 36 MH	52	-	80	8	-	24

PS52

5-YEAR FOLLOW UP OF ABATACEPT THERAPY FOR SYSTEMIC SCLEROSIS WITH CHRONIC ARTHRITIS

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Objective. To assess long term safety and effectiveness of abatacept therapy for systemic sclerosis with chronic arthritis.

Case report. We describe the case of a 76 years old female patient with chronic arthritis anti-CCP and RF positive, though non-erosive, from 2003, refractory to several treatments (failed methotrexate, leflunomide, etanercept, rituximab). She received abatacept 10 mg/kg/month, from december 2008 in association with methotrexate 15 mg weekly. Systemic sclerosis was diagnosed in 1995 and caractherized by limited skin involvement, Raynaud's phenomenon, teleangiectasia, calcinosis, disphagia without documented esophageal dilatation (CREST syndrome). Before starting abatacept the polyarthritis was active with DAS28 5.1. At baseline, antinuclear-centromere antibodies were positive 1:1280. A mild reduction of TLCO (63%) without interstitial lung disease and with normal pulmonary arterial pressure by echocardiography (20 mmHg) were reported.

After the first year of treatment, abatacept induced a significant reduction in swollen and tender joint count, improvement in DAS28 with a EULAR good response (DAS28 1.74). Then we observed a slight increase in DAS28 compatible with a moderate response from december 2011 up to date. No radiological erosion was detected at hands and feet.

Skin involvement remained stable, no digital ulcer occurred. Pulmonary and cardiologic assessment were made every year: mild reduction of TLCO persisted until month 48, then a slight decrease was reported at month 56 (TLCO 49%) without clinical variations and with a mild but non significant increase of pulmonary arterial pressure (32 mmHg) that remained in normal range. No decrease in FVC and TLC was detected. Neither deterioration of esophageal dysmothility nor symptoms of gastrointestinal involvement were reported. Renal function remained in normal range (serum creatinine 1 mg/dl).

Abatacept was well tolerated during 56 months and treatment is still ongoing.

Conclusions. Abatacept proved to be a good treatment also in the long term for systemic sclerosis associated to chronic arthritis. In agreement with previous studies 1 further controlled investigation is worthwhile.

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PS53

WHAT ARE SYSTEMIC SCLEROSIS-RELATED CALCINOSES MADE OF AND CAN WE DISSOLVE THEM?

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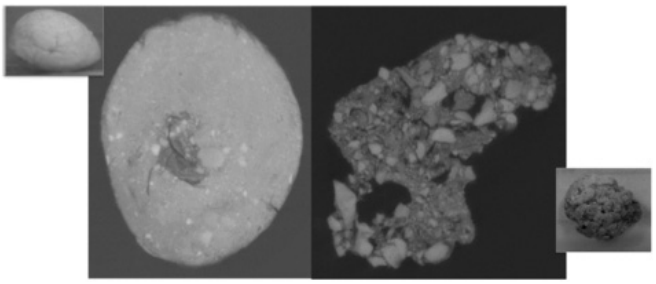
Background and aim. Approximately 25- 40% of patients with systemic sclerosis will develop calcinosis, with the knees, elbows and fingertips being commonly affected.1 There is limited information in the literature on the composition of calcinotic lumps, 2,3 although what is available (mostly X-ray diffraction data, microscopy and thermal analyses) suggests that they consist of B carbonated apatite. The aim of this research was to unite all of these methods and more to provide a complete image of the structure and composition of calcinoses associated with systemic sclerosis with a view to identifying compounds which are able to break them down.

Methods. Micro-computed tomography (XCT), thermal (TGA), powder x-ray diffraction (PXRD), elemental, electron microscopy (SEM) and infra-red (IR) analyses were carried out to determine the elemental composition and internal structure of the deposits. The calcinotic deposits had either extruded spontaneously or were surgically removed. For dissolution studies, samples were covered with a solution of the desired reagent and sonicated. The amount of calcium taken up by the solution was measured by elemental analysis.

Results. Hydroxyapatite (Ca10(PO4)6(OH)2) was the main component of the four samples examined. The presence of carbonate was confirmed by IR and TGA studies. The internal composition of these deposits was probed by SEM and XCT, which show that the samples have very different structures, despite having similar elemental compositions. This is shown in figure 1a, where the sample on the right is visibly more porous than that on the left. The dissolution screening indicated that picolinic and citric acid and selected aminocarboxylate calcium chelators were most effective at breaking down or dissolving the deposits.



Conclusion. Calcinotic deposits were found to consist of hydroxyapatite with a carbonated component. A greater understanding of the composition of these structures could lead to a better understanding of their formation, potential prevention and improved treatment. Citric and picolinic acids and aminocarboxylate compounds were identified as potential compounds for treating calcinosis.

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PS54

ANTICENTROMERE ANTIBODY, DISEASE DURATION AND HISTORY OF SURGICAL DEBRIDEMENTS PREDICT CALCINOSIS IN PATIENTS WITH SYSTEMIC SCLEROSIS

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Background. Calcinosis (subcutaneous deposits of calcium occurring predominantly over pressure points), is a characteristic feature of systemic sclerosis (SSc), occurring in 20-40% of patients. Our aim was to examine clinical and serological associates of SSc-related calcinosis, and whether it is possible to build a model to predict presence of calcinosis.
Methods. This was a retrospective cohort study of patients with SSc attending a tertiary referral centre. Clinical and demographic features were reviewed. The variables examined were: age, gender, disease subtype, duration of SSc, previous intravenous prostanoid infusions, surgical debridement and/or amputation, autoantibody status (anticentromere and antitopoisomerase), pulmonary fibrosis and pulmonary hypertension. Logistic regression was used to investigate associations between demographic and clinical factors and the odds of clinical calcinosis. Variables of interest were then combined in a multiple regression model to obtain adjusted odds ratios and confidence intervals.
Results. A total of 317 patients (86% female, median age 60 years, range 24-91) were included. Ninety-four (30%) had clinically apparent calcinosis. Age distribution, and gender, were similar in those with and without calcinosis. Although a number of predictors suggested themselves during exploratory analysis of the data, only surgical debridements (history of debridements in 30.9% of those with and 8.6% without calcinosis), anticentromere status (positive in 54.3% with and 31.8% without calcinosis) and disease duration (17.0 years with and 10.7 years without calcinosis) remained significant after adjusting for other variables. Therefore a patient who had had debridements was more likely to have calcinosis compared to one who had not (OR [95% CI]: 3.39 [1.61 to 7.13]). Similarly, a patient with anticentromere positivity was more likely to have calcinosis (OR [95% CI]: 2.28 [1.24 to 4.21]). The odds of having calcinosis increased with disease duration (OR [95% CI]: 1.08 [1.04 to 1.11]): the odds of having calcinosis increased by 8% (CI, 4 to 11%) for each year since diagnosis. The specificity of the model was high (correctly classifying a patient who did not have calcinosis 91% of the time), but the sensitivity was relatively low, correctly classifying a patient who did have calcinosis only 35% of the time.
Conclusions. In a cohort of patients with SSc attending a tertiary centre, history of surgical debridement, positive anticentromere antibody and disease duration were predictors of calcinosis. However, the low sensitivity of a multiple regression model suggests there are other important predictors of calcinosis that have not been accounted for in this analysis.

PS55

ANTI-CARBAMYLATED PROTEIN ANTIBODIES ARE PRESENT IN SYSTEMIC SCLEROSIS

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Background. Anti-CarP antibodies, a newly discovered autoantibody system in rheumatoid arthritis (RA), are present in patients with arthralgia and their presence predicts the development of RA independent from anti–CCP antibodies (1). Protein carbamylation, promoted by uremia and inflammation (2), is linked to vascular dysfunction and activation of mesangial cell with consequent collagen deposition and fibrosis (3,4,5). Thus we investigated for the presence of anti-CarP antibodies in patients with systemic sclerosis (SSc), where vascular damage is relevant.
Patients and Methods. We enrolled 48 patients with SSc. The mean age was 59,3 years (range 22–80 years), mean disease duration 116,3 months (range 3–360 months). Twenty-three patients (47,9%) had a diffuse form of the disease and 25 (52%) a limited one.
We found pulmonary fibrosis in 25 (52%) SSc patients, gastrointestinal symptoms in 24 (50%), pulmonary hypertension in 14 (29%), cardiac involvement in 9 (18,75%).
Twenty-eight (58,3%) patients had an articular involvement.
Detection of Anti-CarP antibodies were performed by ELISA according to Shi J *et al*. while rheumatoid factor (RF) was measured by nephelometry.
Results. Eight patients (16,6%) were positive for anti-CarP antibodies, 14 (29%) had RF. In the SSc group of patients anti-CarP positivity was significantly higher than in the control group: 8 (16,6%) patients versus 1 (2%) control (311 UI, range 57–1762, versus 135 UI, range 39–749; $p<0,001$).
We found a significant correlation of anti-CarP antibody serum levels with RF ($p<0,03$). Almost all the anti-CarP antibody positive patients had articular involvement (7/8 patients, 86%), but it didn't gain a statistical significance. No significant correlation was found with any other clinical and laboratory data.
Conclusions. Anti-CarP antibodies are present in patients with SSc and correlates with RF positivity.
Further investigations on a major number of cases are needed to assess the role, if any for these new autoantibodies in this disease.
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Poster Tour 9: *Musculoskeletal System & Rehabilitation*

PS56

THE DEVELOPMENT OF A MODIFIED HAND MOBILITY IN SCLERODERMA TEST AND ITS POTENTIAL AS AN OUTCOME MEASURE IN SYSTEMIC SCLEROSIS

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Objective. To develop the hand mobility in scleroderma (HAMIS) test to a modified HAMIS (mHAMIS) to make the test more feasible and to evaluate its psychometric properties in early systemic sclerosis (SSc) and during long-term follow-up.
Methods. This retrospective study is based on 266 patients previously examined using the original HAMIS. It comprises a cross-sectional part to develop the mHAMIS test, and a longitudinal design, to evaluate the psychometric properties of mHAMIS. Data were stratified into three groups with different disease durations: 1) 0–3 years, 2) 3.1–5 years, and 3) 5.1–9 years after disease onset. Sixty-four patients were assessed in the first group and were included in the longitudinal study. Disease parameters were: skin involvement using disease subset and the modified Rodnan skin score, digital lesions and serum cartilage oligomeric matrix protein (COMP).
Results. Cronbach's alpha with item reduction was calculated separately for each group. Based on these analyses, a mHAMIS test consisting of finger flexion, finger extension, finger abduction and dorsal extension was created. The internal consistency of mHAMIS was: 0.78, 0.83 and 0.73 in the three groups. In the whole study group, mHAMIS showed a significant correlation with hand skin score (rs: 0.44), and was able to discriminate limited cutaneous SSc from diffuse cutaneous SSc (p=0.001). Longitudinal values of the mHAMIS, the hand skin score and serum COMP were closely paralleled, and the change in mHAMIS score between baseline and the first follow-up examination was significantly correlated with the change in hand skin score (rs=.44; p=0.001) and the change in serum COMP (rs=.68; p=0.001).
Conclusions. The mHAMIS involves 4 easily measurable items, and has the potential to be a relevant measure of outcome in the evaluation of the consequences of fibrotic skin involvement in SSc.

PS57

ANALYSIS OF PATIENTS WITH SYSTEMIC SCLEROSIS AND RHEUMATOID ARTHRITIS OVERLAP SYNDROME

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Introduction. Joint involvement is a common clinical feature in patients with systemic sclerosis (SSc), however, a true overlap with rheumatoid arthritis (RA) is rarer.
Purpose. The aim of the present work was to investigate prevalence, clinical and therapeutic approach as well as the serological profile of a series of SSc-RA patients.
Patients and methods. Of the 439 patients with SSc evaluated at our clinic, we retrospectively identified those who have an overlap syndrome and then we analyzed the main epidemiological, clinical and serological features of patients with SSc-RA.
Results. We identified 68 patients with overlap syndrome, including 18 with RA. Table I shows the main features of the patients with SSc-RA compared with those without RA.
There were no significant differences between the two groups in the prevalence of diffuse cutaneous SSc (26.3% in SSc-RA versus 28%), in the organ involvement (heart, lung and esophagus) and in the prevalence of digital ulcers.
The prevalence of anticentromere antibody (ACA) was lower in overlap SSc-RA (22.3% vs 47%, p0.06). SSc patients with RA developed arthralgia prior to Raynaud's phenomenon at a significantly higher incidence than those without (72% versus 25%, p<0.001).
In 60% of the patients the diagnosis of RA was subsequent to SSc onset, in 20% the diagnosis antedated SSc and in 20% was made in the same year. Eight of the 12 patients (75%) had erosive arthritis.
Rheumatoid factor (FR) and anti-citrullinated protein antibodies (ACPA) were more significantly higher in patients with SSc-RA (55.5% vs. 10.7%, p<0.001; 27.2% vs. 0.45%, p<0.001, respectively).
SSc-RA overlap syndrome subjects were compared with a group of patients with RA alone matched for age, sex and disease duration. Between the two groups there were no significant differences in the therapeutic approach (use of biological drugs and total dose of glucocorticoids). In boths groups the most used DMARDs were Methotrexate, Hydroxychloroquine and Leflunomide.
Discussion. The data of our study confirm those present in the literature. RA is one of the most common overlap disease in SSc patients (4,1%). RA doesn't seem to have a significant impact on the disease features of SSc. Furthermore SSc-RA patients seem to have a disease profile similar to RA subjects without SSc, as the therapeutic approach shows no difference.

Table I. Epidemiological features ofSSc-RA as compared to SSc non RA subjects.

	SSc with RA N 18	SSc without RA N 421	*p*
male.female	1:17	1:11	NS
Age, years (mean + ds)	64.12±10.99	59.25±14.23	NS
Age at onset of SSc, years (mean + ds)	52.31±13.66	49.88±14.77	NS
Age at onset of RA, years (mean+ ds)	54.47±13.37	-	
Duration of SSc, years (mean + ds)	10.81±9.74	10.14±9.2	NS
Duration of RA, years (mean + ds)	7.80±10.72	-	

PS58

ANTI-CCP ANTIBODIES AND RHEUMATOID FACTOR IN SYSTEMIC SCLEROSIS – PREVALENCE AND USEFULNESS

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Introduction. It is known that a-CCP antibodies and rheumatoid factor (RF) are the main tools to diagnose rheumatoid arthritis (RA). In systemic sclerosis (SSc), arthralgia are common manifestation but arthritis occurs rather rare. According to literature a-CCP antibodies and RF may be present in SSc, particularly with joint involvement.
The aim. The aim of the study was to assess the prevalence and usefulness of a-CCP antibodies and RF IgM in two groups of patients (pts) with SSc (limited cutaneous - lcSSc and diffuse cutaneous – dcSSc).
Material and Methods. The study was performed in 126 (99-female and 27-male) consecutive SSc patients treated in Department of Rheumatology, fulfilled the ACR classification criteria of SSc (57 diffuse SSc-dcSSc and 69 limited SSc –lcSSc). The mean age 53.5±13.11 years (range 18-81). The mean disease duration 6.27±6.02 years (range 0.1-23). A-CCP antibodies and RF in IgM class were determined using a ELISA commercial test. The different clinical and serological features of SSc was determined.
Result. According to our observation: 107/126 (80%) SSc pts had joint manifestations (arthralgia or arthritis), 38/126 (30%) SSc pts had arthritis and 8/126 (6.6%) had overlap syndrome (SSc- RA). The mean disease activity score28 (DAS 28) in group with SSc-RA was 4.46±1.29. A-CCP antibodies was found in 10 of 89 (11.2 %) SSc pts and RF IgM in 59 of 89(66%) pts. In group with joint involvement the a-CCP was present in 9 of 78 (11%) pts and RF in 54 of 77 (70%) pts. 1 of 10 (10%) pts had positive a-CCP antibodies and 4 of 13 (31%) pts had positive RF in SSc group without joint manifestations. In group with arthritis a-CCP antibodies was present 7 of 31 (22.6%) and RF was present in 20 of 28 (71%) pts. The significant higher titers of a-CCP antibodies (p=0.007), RF IgM (p=0.038), erythrocyte sedimentation rate (ESR) (p=0.019) and CRP (p=0.032) were observed in SSc group with arthritis compare to group without arthritis. Significant correlation was found between the group of SSc pts with arthritis and presence of a-CCP antibodies (p=0.013, ϕ =0.263) and between the group of SSc pts with arthralgia and presence of RF IgM (p=0.025, ϕ= 0.238). No relationship was observed with arthritis and presence of RF IgM in SSc group.
Conclusions. 1. The prevalence of rheumatoid factor is common in systemic sclerosis. 2. In systemic sclerosis rheumatoid factor correlate with arthralgia and a-CCP antibodies correlate with arthritis.

PS59

EFFECTS OF PRESSURE RELIEVING INSOLES FOR FOOT PROBLEMS IN PEOPLE WITH SSC: THE PISCES RANDOMIZED CONTROLLED TRIAL

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Background. Foot problems associated with systemic sclerosis (SSc; scleroderma) are common and disabling.
The objective of this randomized controlled trial was to evaluate whether foot pain and foot-related health status in SSc can be improved through the provision of a simple pressure-relieving and insulating insole.
Methods. A multicentre RCT conducted in four UK participating centres. A total of 141 consenting patients with confirmed SSc and plantar foot pain were randomised to receive either a commercially available pressure-relieving thermally insulating insole or a sham insole. Randomisation on a 1:1 basis was performed centrally.
The primary end point was a reduction in pain measured using the 100mm pain subscale of the Foot Function Index, after 12 weeks of intervention. Sample size was determined a priori based on a requirement to detect a 15mm difference (SD 25.7, alpha =0.05 and power =90%).
In a subset of 49 patients at the lead centre, plantar pressure measures (maximum mean pressure at heel and forefoot, with and without insoles in situ) were also obtained.
Results. One hundred and thirty patients provided valid data for the primary endpoint. In both groups there was a systematic improvement in FFI pain subscale scores from baseline to 12 weeks (Active group -13.1mm, 95%CI -18.66 to-7.55; Sham group -10.7, 95%CI -16.17 to -5.28). An ANCOVA model adjusting for centre, gender and baseline FFI score confirmed no difference in effect between the intervention and sham groups (difference=-2.4, 95%CI -7.70 to 2.94, p=0.3778). Compared to a shoe-only baseline measure, the pressure was lowered in the heel region by use of the active insole (median difference (range) -24kPa (-75,22)) compared to the sham -4.6kPa ((-23,10), (p<0.01)), but in the forefoot the difference between insole types was not significant; pressure change -17.2 kPa (-61,19) for the active insoles and -10.8kPa (-39,0) for sham insoles (p=0.31).
Conclusions. The study compared a simple therapeutic insole with a sham device and found that over 12 weeks both produced a clinically worthwhile improvement in patient reported foot pain but with no difference between intervention arms. The active device produced a significantly greater reduction in pressure than the sham at the heel although not at the forefoot. This exploratory analysis suggests therefore, that despite careful selection the sham device introduced some unintended physical effect. The difficulty with employing a true sham as a control in physical intervention trials such as this may suggest the need for a zero intervention arm for similar studies in future.

PS60

HAND DISABILITY IN PATIENTS WITH SYSTEMIC SCLEROSIS: THE ROLE OF AN INDIVIDUALIZED REHABILITATION PROGRAM

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Introduction. Hand is often the first site of clinical manifestation of systemic sclerosis (SSc) and its function can be compromised not only by skin thickening but also by vascular injury and local tissue, joint and tendon inflammation. Patients may experience loss of joint mobility that interferes with everyday activities and can cause severe disability.The aim of the present study was to evaluate the results of an individualized hand rehabilitation program in 27 patients with SSc.
Patients and Method. Twenty-seven consecutive patients (herefrom defined as cases) with a diagnosis of SSc made according to the criteria of LeRoy, who attended our outpatient or daycare clinic (Trento) were enrolled. The main demographic and clinical characteristics of the 27 cases are shown in Table I. Twenty-five controls were recruited from another Rheumatology Unit (Modena). There was no significative difference in the demographic and clinical characteristics between cases and controls. The case group underwent a rehabilitation program consisting of 19 individual sessions of 45 minutes, every day for the first week and then two days a week for the subsequent 7 weeks. Each session included a combination of finger and wrist stretching and strengthening exercises, massages and occupational therapy. The outcomes considered were the Health Assessment Questionnaire (HAQ), the Hand Anatomic Index (HAI) and the Hand Mobility in Scleroderma (HAMIS) test. Both cases and controls underwent evaluation by the same examiner at baseline (T0) and after two months (T2); the cases were also evaluate at 12 months (T12). Non-parametric test were used for all the statistical analysis, for more clarity data in tables were expressed as mean and standard deviation. The level of statistical significance was set at $p<0.05$.

Table I. Main demographic and clinical characteristics of cases (n=27)

Age*, yrs		63.9 (12.4)
Female, n (%)		23 (85.2)
Disease duration*, yrs		6.7 (2.4)
Disease subset	IcSSc, N (%)	16 (59.3)
	dcSSc, n (%)	11 (40.7)
Autoantibodies	ANA, n (%)	8 (29.6)
	ACA, n (%)	8 (29.6)
	Anti-Scl70, n (%)	11(40.7)
TSS*		7.7 (4.2)
Ulcers, n (%)		11 (40.7)
ILD, n (%)		16 (59.3)
DLCO*, (%)		65.4 (19.6)
PAH, n (%)		2 (7.4)

*Continuous data are espressed as mean (standard deviation).
IcSSc: limited cutaneous Systemic sclerosis; dcSSc. diffuse cutaneous Systemic sclerosis; ACA: anticentromere antibodies; Anti-Scl70: anti-Scl70 antibodies; TSS: modified Rodnan total skin score; DLCO: diffusing capacity for carbon monoxide, % predicted; PAH: pulmonary artery hypertension.

Table II. Variations of measured parameters in cases treated with a rehabilitative program and controls.

	Mean (standard deviation)			*p**	
	T0	T2	T12	T0-T1	T0-T12
Cases (n=27)					
HAQ*	0.88 (0.76)	0.72 (0.65)	0.85 (0.83)	0.014 ns	
HAI dx	3.10 (1.05)	3.43 (1.04)	3.26 (1.21)	<0.001	ns
HAI sx	3.48 (1.05)	3.85 (0.99)	3.58 (1.07)	<0.001	ns
HAMIS	10.11 (9.53)	7.78 (9.28)	7.56 (8.66)	<0.001	<0.001
Controls (n=25)					
HAQ	0.73 (0.85)	0.74 (0.84)	-	ns	-
HAI dx	3.44 (1.31)	3.43 (1.33)	-	ns	-
HAI sx	3.64 (1.19)	3.58 (1.10)	-	ns	-
HAMIS	9.16 (10.10)	9.28 (10.28)	-	ns	-

*Wilcoxon signed rank test.
T0: baseline; T2: two months; T12: twelve months; HAQ: Health Assessment Questionnaire; HAI: Hand Anatomic Index; HAMIS: Hand Mobility in Scleroderma; ns: not significant.

Results. At baseline there was no significant difference in HAQ, HAI and HAMIS between cases and controls. We found that at baseline HAQ of both cases and controls correlate significantly with hand function parameters: HAI dx ($r=-0.43$, $p=0.001$), HAI sx ($r=-0.40$, $p=0.003$), and HAMIS ($r=0.58$, $p=<0.001$). In the case group the rehabilitation program was associated with a significant improvement of both HAQ and hand function outcomes at 2 months. At 12 months only HAMIS remained significantly improved (Table II).
Discussion. Our study shows that in SSc patients hand function correlates with HAQ and that an individualized rehabilitation program can improve both parameters. The benefit was only partially mainteined at twelve months, therefore it could be useful to repeat the program at least yearly.

PS61

SYSTEMIC SCLEROSIS-RELATED SYNOVITIS: IMAGING FEATURES AND HISTOLOGICAL EXAMINATION OF THE SYNOVIAL TISSUE

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Previous studies have shown an increased prevalence of synovitis and tenosynovitis in systemic sclerosis (SSc) as detected by musculo-skeletal ultrasound (US) or magnetic resonance imaging (MRI). The histological correlate of synovitis detected by imaging is not yet known as synovial biopsies were not available in these studies.
We aimed to assess the inflammatory and non-inflammatory lesions in synovial biopsies in patients suffering from SSc-related arthritis.
Seven synovial biopsies from 4 SSc patients (2 diffuse and 2 limited SSc) were obtained. Three patients had paired synovial biopsy before and after immunsupressor treatment shift and one patient had a single biopsy before starting immunosupressor therapy. Five knee biopsies and two wrists biopsies were analyzed by immunohistochemistry (IC). Imaging studies (MRI, US and/or arthroscopy) were performed prior to biopsies.
Disease duration from the Raynaud phenomena to the first synovial biopsy was 1-14 years. All patients had oligoarthritis at the time of the first biopsy. Imaging studies confirmed the presence of synovitis with increased synovial thickness and areas with hypervascularisation. In addition, in one patient, intra-articular calcifications were observed. Microscopic examination of the synovium revealed increased thickness and altered global architecture with marked angiogenesis, inflammatory cell infiltrates, increased collagen deposition and extracellular deposits. The increased thickness of the synovium was due both to increased deposition of collagen and infiltrates of inflammatory cells. These changes paralleled those observed by imaging and correlate with the duration of arthritis. IC revealed an increased density of T lymphocytes and macrophages with low density of B-cells and plasmocytes. Peri-vascular T-cell infiltrates and T-cells aggregates around inflammatory nodules were present, the latter being associated with marked deposits of non-collagen, amorphous material. Angiogenesis consisted mainly in increased density of immature vessels as detected by WT1 immunostaining. Arteriolar onion-skin like lesions were present in biopsies from more severe patients. At the time of the second biopsy, persistent arthritis was noted despite changes in immunupressor therapy. Paired synovial biopsies confirmed the persistency of abnormal synovial findings.
The histological correlate of joint involvement is shown to be synovitis in which the synovium is invaded by an inflammatory lymphocytic infiltrate, macrophages and immature vessels. Both inflammatory and non-inflammatory changes are present in the synovium from SSc patients including increased vascularity, collagen deposition and fibrosis. This pattern is distinct from that described in lupus arthritis, rheumatoid arthritis, psoriatic arthritis and osteoarthritis.

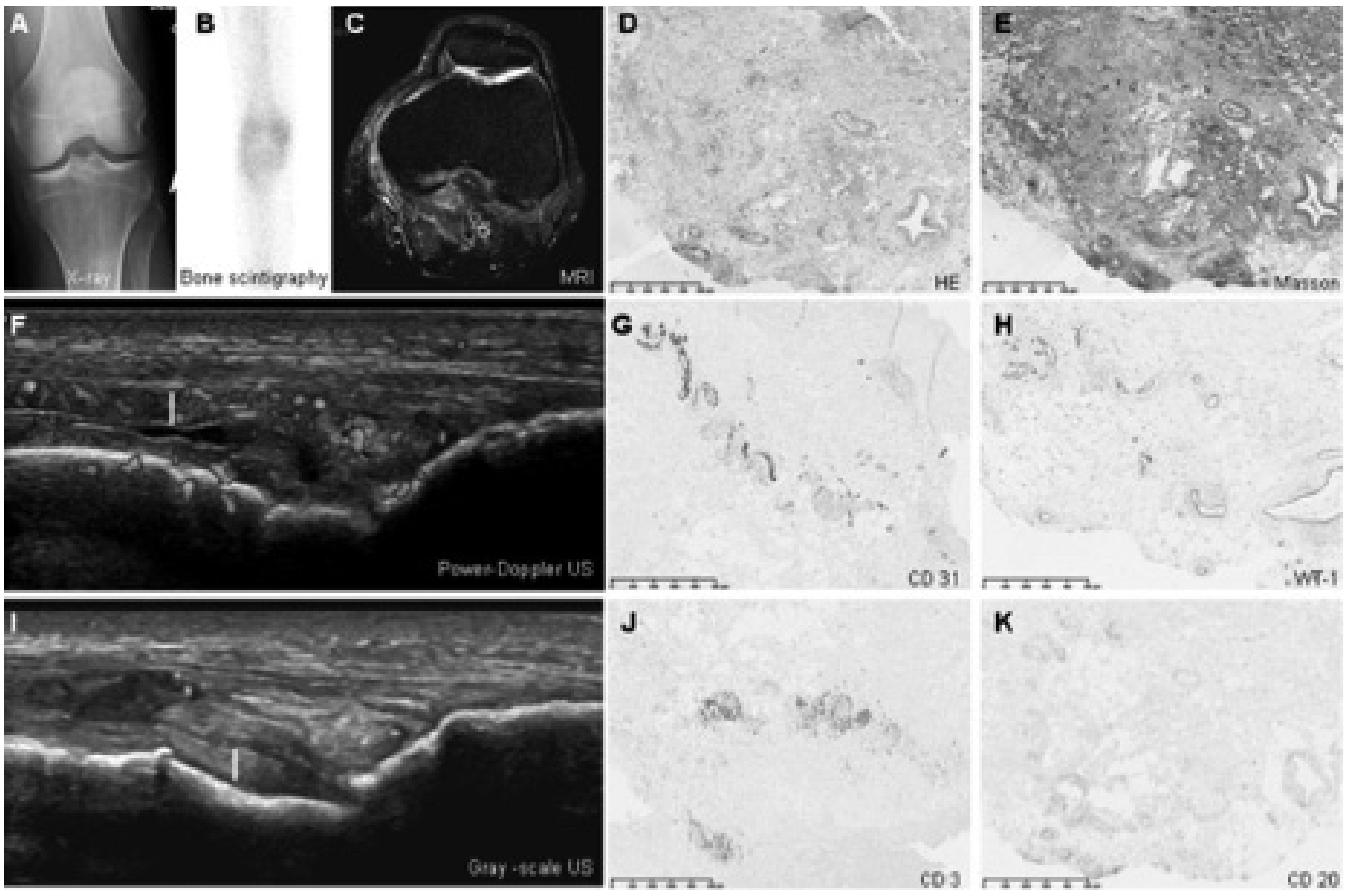

Fig. 1. Imaging studies and immunohistochemistry characterization of the synovial biopsy in a 43 years old patient suffering from bilateral knee arthritis related to diffuse SSc.

Poster Tour 10: *Upper and Lower Gastrointestinal/nutrition*

PS62

EVALUATION OF THE PATIENT-REPORTED OUTCOMES MEASUREMENT INFORMATION SYSTEM (PROMIS®) GASTROINTESTINAL (GI) SYMPTOMS MEASURES IN SYSTEMIC SCLEROSIS (SSC)

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Introduction. The National Institutes of Health PROMIS® roadmap initiative is a cooperative research program designed to develop, evaluate, and standardize item banks to measure patient-reported outcomes (PROs) across different medical conditions as well as the US population (www.nihpromis.org). As part of the National Institutes of Health PROMIS® roadmap initiative, we developed GI Symptoms measures that assess 8 domains: Gastroesophageal reflux (13 items), disrupted swallowing (7 items), diarrhea (5 items), bowel incontinence/soilage (4 items), nausea and vomiting (4 items), constipation (9 items), belly pain (6 items), and gas/bloat/flatulence (12 items). All scales are calibrated using a two-parameter IRT graded response model and scored on a T-score metric with a mean of 50 and SD of 10 in the U.S. general population. This paper evaluates the construct validity of the GI measures in patients with SSc.
Methods. 165 patients with SSc were administered the PROMIS GI Symptoms measures and UCLA SCTC GIT 2.0 instrument. GIT 2.0 has 5 symptom scales: reflux, distention/ bloating, diarrhea, constipation, and fecal incontinence. Product-moment correlations of the PROMIS GI measures with the GIT 2.0 symptoms scales were used to evaluate construct validity. In a subset of patients (N=37), both instruments were administered at 2 time points. F-statistics was calculated from one-way ANOVAs to assess responsiveness to change
Results. Patients with SSc GI involvement had scale scores 0.2-0.7 SD worse than US population. Hypothesized correlations were larger than other scales and in the right direction (Table). F-statistics were greater for 6 of 8 PROMIS scales (range 0.45 for belly pain to 3.21 for reflux scale) vs. GIT 2.0 except for diarrhea scale (0.67 vs. 0.98 for GIT 2.0) and constipation scale (1.37 vs. 1.79 for GIT 2.0).
Conclusion. PROMIS GI Symptoms scales are significantly correlated with the hypothesized GIT 2.0 scales and 6 of 8 scales showed greater responsiveness to change than the GIT 2.0.

Table. Product-moment correlations between PROMIS GI Symptoms scales and UCLA SCTC GIT scales.

	Reflux*	Distention/ bloating	Diarrhea	Constipation	Fecal Incontinence
Reflux	**0.77**	0.44	0.13	0.25	-0.03
Disrupted swallowing	**0.61**	0.39	0.16	0.21	0.13
Nausea and vomiting	**0.66**	0.44	0.20	0.22	0.18
Belly pain	0.45	0.49	0.23	0.34	0.04
Gas/bloat/flatulence	0.46	**0.73**	0.30	0.29	0.10
Diarrhee	0.25	0.25	**0.65**	0.02	0.54
Constipation	0.37	0.32	0.05	**0.76**	-0.01
Fecal Incontinence	0.12	0.11	0.43	-0.18	**0.87**

*GIT 2.0 Reflux scale about reflux, dysphagia to solid foods, and nausea/vomiting.

PS63

UPPER GASTROINTESTINAL BLEEDING PREDICTS HIGHER MORTALITY IN SYSTEMIC SCLEROSIS PATIENTS

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Background. The gastrointestinal tract is involved in nearly all patients with systemic sclerosis (SSc) and is a source of great morbidity and even mortality.
Aim: To assess whether there is correlation between upper gastrointestinal (UGI) endoscopy findings and mortality in SSc patients.
Methods. The records of 256 SSc patients seen in our rheumathologic clinic between the years 2003-2013 were reviewed. 140 patients who had at least one detailed endoscopic report and at least 6 months follow-up were included in the study. Patients data included demographic details, type of SSc, disease duration, modified Rodnan skin score (mRSS).
Endoscopic findings that were included in the analysis were esophagitis, ulcerations, tumors, gastric antral vascular ectasia (GAVE), gastric erosions, submucosal hemorrhages and lumen bleeding. The statistical methods used included descriptive statistics, T test, Spearman's correlation and multiple logistic regression analysis.
Results. Forty seven patients (16 diffuse SSc) had evidence of GAVE or antral erosions and hemorrhage. The mortality rate in this group, during the follow up was 37%, compared to 25% in the group of 93 (39 diffuse) SSc patients without endoscopic evidence of GAVE or UGI bleeding (p=0.009). There were no statistical differences between the groups regarding age (mean (SD) 55(13)years versus 55(14) years. The mRSS was higher in the group with UGI bleeding (mean (SD) 8(7) versus 5.6(4), but it did not reach statistical significance. The disease duration was shorter (mean (SD) 6.5(5.8) years versus 10.5(6.5)) – p<0.05.
Esophagitis was found in 90% of patients. All patients were under PPI treatment.
Conclusions. A diagnosis of GAVE or UGI bleeding on endoscopy was associated with higher mortality, in our cohort. Shorter disease duration might be correlated with more aggressive course

PS64

NUTRITIONAL SUPPORT IN PATIENTS WITH SYSTEMIC SCLEROSIS

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Systemic sclerosis (SSc) is a multisystem autoimmune disease which involves gastrointestinal tract in about 90% of cases. It may contribute to nutritional deterioration.
Objective. To assess whether the application of a nutritional support protocol (1) to these patients could improve their nutritional status.
Methods. Unicentric prospective study, performed on an outpatient basis, in a county hospital. "Malnutrition universal screening tool" (MUST) was used to screen risk for malnutrition. Weight, height, energy and protein requirements, macronutrient intake and nutritional biochemical parameters were evaluated. Nutritional intervention was performed in patients at risk for malnutrition (MUST above 1) every three months until 1 year.
Results. Of the 72 patients, 9 (12.5%) were at risk for malnutrition. Iron deficiency anemia (18.35%) and vitamin D deficiency (54%) were the most frequently observed nutritional deficits.

Data (mean + DS) (n=9)	Baseline	12 months
Weight (kg)	51.5±8.5	54.3±9.1
BMI (kg/m2)	21.6±2.5	22.0±3.2
Energy intake (Kcal)	1487±203	1876±175
Protein intake (g)	67±12	75±19
Carbohydrates (%)	39.9±7.18	43.7±4.3
Proteins (%)	18.2±1.7	16.2±2.8
Fats (%)	40.5±6.2	39.9±2.5
Fiber (g)	15.4±6.6	24.3±14.8
Hemoglobin (12-16 g/dl)	11.73±1,89	12.55±1.83
Vitamin D (>30ng/ml)	21.5±8,87	27.3±1.78
Albumin (35-52 g/dl)	38,78±2.03	40±2.82
Ferritin (30-400 ng/ml)	59.5±37.7	52±39.5

Conclusions. Dietary intervention was able to improve body weight and food intake. Hemoglobin values and vitamin D deficiency improved with iron and vitamin D supplements.
References
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PS65

VASCULAR EVENTS ARE RISK FACTORS FOR ANAL INCONTINENCE IN SYSTEMIC SCLEROSIS: A STUDY ON MORPHOLOGY AND FUNCTIONAL PROPERTIES AS MEASURED BY ANAL ENDOSONOGRAPHY AND MANOMETRY

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Objectives. The aim of the study was to study the anal sphincter morphology, anal sphincter pressure and the rectoanal inhibitory reflex in patients with systemic sclerosis (SSc) complicated by anal incontinence (AI) and to investigate possible risk factors for AI in SSc.
Methods. 19 SSc patients with severe AI were investigated using anal endosonography, anal manometry, and rectal manovolumetry. To determine risk factors for AI, data concerning disease characteristics for each SSc patient with AI were compared to 5 SSc patients without AI.
Results. Mean (SD) internal sphincter thickness was 1.3 (0.46) mm in patients with AI which was thinner (p<0.001) than reference data from healthy individuals whose internal sphincter measured 2.2 (0.45) mm whereas external sphincter thickness did not differ. Mean (SD) resting pressure in AI patients was lower than reference data from healthy individuals (60 (22) vs 94 (29) mmHg, p<0.002), whereas squeeze pressure did not differ. Centromeric antibodies, and features of vascular disease, ie presence of pulmonary arterial hypertension, digital ulcers, pitting scars or the need for Iloprost infusions were associated with AI, whereas fibrotic manifestations, ie modified Rodnan skin score, the diffuse cutaneous SSc subset or low vital capacity were not.
Conclusions. SSc patients with AI have a thin internal anal sphincter and a low resting pressure. Risk factors for AI among SSc patients are centromeric antibodies and vascular disease which supports the hypothesis that gastrointestinal involvement in SSc is in part a vascular manifestation of the disease.

PS66

FAECAL LEVELS OF CALPROTECTIN IN SYSTEMIC SCLEROSIS ARE STABLE OVER TIME AND ARE HIGHER COMPARED TO PRIMARY SJÖGREN'S SYNDROME AND RHEUMATOID ARTHRITIS

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Introduction. Faecal calprotectin (FC) has been proposed to be a biomarker of gastrointestinal (GI) disease in systemic sclerosis (SSc). The purpose of this study was to extend cross-sectional observations and prospectively assess the variability of FC over time in SSc patients. We also aimed to examine FC in relation to immunosuppressive therapy. Finally we wanted to analyse FC in other rheumatic diseases to evaluate the specificity of FC for SSc GI disease.
Methods. FC was measured in consecutive patients with SSc, primary Sjögren's syndrome (pSS), rheumatoid arthritis (RA) and in healthy hospital workers. The intraindividual variability of FC in SSc was assessed with intra class correlation (ICC) and κ statistics. Associations between FC and objective markers of GI disease and immunosuppressive medication were investigated.
Results. FC was associated with micronutrient deficiency and GI pathology as assessed by cineradiography confirming our previous results. FC showed only a limited intra-individual variation in SSc, ICC=0.69 (95% CI: 0.57-0.78) and κ=0.64 (95% CI: 0.56-0.73). Generalised immunosuppression did not have any significant impact on FC. FC was significantly higher in SSc patients compared to patients with pSS or RA as well as compared to healthy subjects.
Conclusions. FC is a promising non-invasive biomarker for GI disease in SSc. In view of stable levels over time, FC could be a useful marker when novel, more specific drugs targeting the GI tract in SSc will be introduced.

PS67

GASTROINTESTINAL MUCOSAL ABNORMALITIES USING VIDEOCAPSULE ENDOSCOPY IN SYSTEMIC SCLEROSIS

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Objective. The aims of this prospective study were to: 1) determine both prevalence and characteristics of gastrointestinal mucosal abnormalities in unselected patients with SSc, using videocapsule endoscopy; and 2) evaluate whether the presence of gastrointestinal mucosal abnormalities is associated with clinical digestive manifestations, findings of gastric mucosal damage on gastroscopy, esophageal motor impairment as well as extra-digestive manifestations of SSc.
Methods. 50 consecutive patients with SSc underwent videocapsule endoscopy. All SSc patients also completed questionnaires for digestive symptoms.
Results. The prevalence of gastrointestinal mucosal abnormalities was 52% in our SSc patients. Vascular mucosal lesions were predominant, including: 1) watermelon stomach (n=9), 3 of these latter patients exhibited antral gastritis on gastroscopy 2) gastric and/or small intestinal telangiectasia (n=7); and 3) gastric and/or small intestinal angiodysplasia (n=10). We observed a marked correlation between gastrointestinal vascular mucosal lesions and: 1) the presence of anti-centromere antibody (p=0.01); and 2) the absence of anti-Scl 70 antibody (p=0.007).
Conclusion. Our study underscores the usefulness of videocapsule endoscopy in identifying gastrointestinal mucosal abnormalities in 52% of our patients with patients. Moreover, our series highlights that gastrointestinal vascular lesions were predominant in our patients, occurring at early stage of SSc (<3 years). Interestingly, our findings underline that videocapsule endoscopy should be performed to disclose the presence of small intestinal vascular lesions (telangiectasia, angiodysplasia) in: 1) SSc patients with normal gastroscopy; and 2) persistently anemic watermelon stomach patients with SSc in whom, after appropriate endoscopic treatment, gastroscopy shows only mild remanence of antral vascular ectasia.

PS68

ASSESSMENT OF VALIDITY OF GASTROINTESTINAL MORPHOLOGY PROCEDURES AND BACTERIAL OVERGROWTH TESTS USED IN SYSTEMIC SCLEROSIS, BASED ON OMERACT CRITERIA

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Background. The gastrointestinal tract (GI) is involved in nearly all patients with systemic sclerosis (SSc) and is a source of significant morbidity and mortality. There is no single objective measure to assess the extent and severity of GI involvement in SSc patients. The evaluation of the regional morphology and motility and absorptive/ secretory functions of the GI tract by dedicated tests, provides a systematic approach to the assessment of GI involvement in SSC Only validated measures enable scientific research of the disease outcome and the effect of therapeutic interventions.
Objectives. To assess the validity of the morphology and bacterial overgrowth measures used to examine the GI tract in SSc, using the OMERACT criteria.
Methods. We performed a systematic literature search for published data on GI involvement in SSc, using the PubMed database for English-written articles and the Cochrane library from 1966 through the end of 2012. The keywords used were "systemic sclerosis" (SSc) and "scleroderma "and they were combined with text words such as esophagus, stomach, small bowel, colon, anorectal, malabsorption, bacterial overgrowth and procedures used for morphology and bacterial overgrowth assessment (eg endoscopy, breath test, ultrasound, lactulose test, xylose test, barium studies, mucosal biopsy), randomized controlled studies (RCT), clinical studies. Articles obtained from these searches were reviewed for additional references. Case reports or case series of less than 8 patients, articles with non separable data for SSc patients and reviews were excluded. The validity of the tests was evaluated according to the OMERACT principles.
Results. The search identified 468 titles or abstracts. Only 58 articles which answered the inclusion criteria and demonstrated at least one type of validation, were included. Of the 21 morphology, malabsorption and bacterial overgrowth tests examined only 5 tests (gastroscopy, UGI barium studies, mucosal biopsy, hydrogen and methane breath tests and 72 hours fecal fat test) are fully validated. There are a number of partially validated measures, including small bowel follow-through, colonoscopy, endoluminal MRI, endoanal US, jejunal cultures, xylose and lactulose tests.
Conclusions. Technologic advance lead to the introduction of new tests in GI assessment with better spatial and temporal resolution. However only a minority of morphology, malabsorption and bacterial overgrowth tests are partial or fully validated in SSc, conforming OMERACT principles. Proper validation in SSC of the modalities reviewed will provide valuable tools to improve our understanding of SSC and to be used as outcome measures in interventional studies.

Poster Tour 11: *Pregnancy & Sexual Problems*

PS69

SEXUAL DYSFUNCTION: THE PHYSICAL AND PSYCHOLOGICAL BURDEN ON WOMEN IN SYSTEMIC SCLEROSIS

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Background. Systemic Sclerosis (SSc) is a multisystem connective tissue disease associated with significant mortality predominantly as a consequence of cardiopulmonary complications but it is also associated with significant comorbidities including sexual dysfunction. The aims of this study were to evaluate the prevalence of the problem amongst women with SSc from a major single-centre in UK, the impact of SSc on sexual relationship and difficulties faced.
Method 100 women with limited (lcSSc) or diffuse (dcSSc) scleroderma were invited to complete a validated Female Sexual Function Index(FSFI) questionnaire that examined six major domains: desire, orgasm, arousal, lubrication, satisfaction and pain. The questionnaire was broadened to evaluate the psychological effects of sexual difficulties in interpersonal relationships including health professionals.
Results. 50% responded to the questionnaire of which 52% had diffuse disease subset with mean age (±SD, years) 56±1.41. Mean disease duration is similar for both disease subsets with (mean ±SD, years) 12±2.8. 54% of the patients developed sexual difficulties after their diagnosis and the mean duration from SSc diagnosis to first sexual complaint was (mean, ± SD, years) 4.0±5.8. 84% of the patients reported significant sexual problems in the overall FSFI domains. 60% of the affected women revealed that their sexual complications had inflicted strain in their relationships leading to reduction of activities shared, emotional and financial changes. Some patients even reported breakdown in relationship as a consequence of sexual dysfunction. 46% of the subjects were able to discuss their sexual concerns with their partners, whilst 30% chose not to as they wish to keep these issues to themselves or felt embarrassed to discuss about their difficulties.Among the 32 (64%) women who discussed the problems with their partners, 56% found it to be helpful. 76% of the subjects reported that they had never been asked about sexual health by health professionals. However 52% revealed that they would have discussed their sexual problems if they were concerned. Interestingly 72% of these women admitted to not raising any concern about their sexual problems.
Conclusion. Our study showed that sexual dysfunction is common among women with SSc and presents a major burden for them and their partners physically and psychologically. It is often neglected by the patients and not openly discussed with partners and health professionals. Multidisciplinary teams treating scleroderma patients should be aware of and actively enquire about sexual health as it is a subject worth exploring so that patients' quality of life can be improved.

PS70

IN WOMEN WITH SYSTEMIC SCLEROSIS, SEXUAL FUNCTION IS AFFECTED BY DISEASE-RELATED AND PSYCHOLOGICAL CONCERNS

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Objective. In Systemic Sclerosis (SSc) patients, sexual function is somewhat impaired. Our aim is to evaluate sexual function in women with SSc in comparison to controls and to investigate the association with socio-demographic and disease characteristics, physical and psychological variables.
Methods. 46 women with SSc (age: 56.1 ± 12.4 years; 29 with lSSc, 17 with dSSc) and 46 healthy women (age: 52.0 ± 9.0 years) were assessed for socio-demographic characteristics, gynecological anamnesis and administered with Female Sexual Function Index (FSFI), Short Form-36 (SF36), Health Assessment Questionnaire (HAQ), Hospital Anxiety and Depression Scale (HADS), Rosenberg Self-Esteem Scale (RSES), Coping Orientation to Problems Experienced-New Italian Version (COPE-NIV), Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F).
Patients were also assessed for disease duration and subset, Female Sexual Function in SSc (FSFS), Hand Mobility In Scleroderma Test (HAMIS), Cochin Hand Functional Disability Scale (CHFDS), Mouth Handicap in Systemic Sclerosis Scale (MHISS), Disability Sexual and Body Esteem Scale (PDSBE); fist closure, hand opening and mouth opening.
Results. In SSc patients, only FSFI desire subscale score was significantly lower (p=0.035) versus controls. FSFI scores were not different in dSSc versus lSSc patients (P=NS).
Total FSFI score, similar to controls, by bivariate analysis was negatively correlated with age (p=0.014), HADS-d (p<0.001), FACIT-F (p=0.044), COPE-NIV Avoidance Strategies subscale (p=0.012); and positively related with PDSBE (p<0.001), SF-36 summary mental index (p=0.006) scales. FSFI total score was also negatively correlated to HAQ (p=0.022), total MHISS (p=0.038) and HAMIS (p=0.037) scores.
At multivariate analysis, in SSc, the factors independently associated with FSFI were vaginal dryness (B=-0.72; p<0.001), PDSBE (B=0.42; p=0.001) and HADS depression scale (B=-0.23; p=0.035). Together, these variables explained 70% of the variance in total FSFI.
At multivariate analysis in healthy participants, the factors independently associated with FSFI were age (B=-0.47; p=0.001), FACIT-F (B=-0.36; p=0.006), physical problems PP subscale of SF-36 (B=0.29; p=0.02) and COPE-NIV transcendental orientation scale (B=-0.24; p=0.037), together, explaining 44% of the variance in total FSFI.
Conclusion. In SSc, sexual function, although not different from controls, is influenced by specific disease-related and psychological concerns, different from variables affecting sexual function in healthy controls. Thus, it should be included in patients evaluation and assessed in daily practice.

PS71

SEXUAL DYSFUNCTION IS ASSOCIATED WITH ANXIETY AND HIGHER BODY MASS INDEX IN WOMEN WITH SYSTEMIC SCLEROSIS

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Introduction. Impaired sexual function and limited sexual activity appear to be common among women with chronic illnesses, including Systemic Sclerosis (SSc). Physical and psychological consequences of the disease may be severe and their potential impact in the patient's sexual function is often neglected.
Objective. To evaluate sexual function in patients with SSc and its relationship with biological and psychological aspects of the disease experience.
Methods. A total of 36 SSc women were assessed. A standardized questionnaire was used to register demographic parameters, current therapies and clinical manifestations of SSc. Sexual function was assessed by self report using of the Female Sexual Function Index (FSFI), which evaluates 6 different sexual domains referring to the previous 4 weeks: Desire, Arousal, Lubrication, Orgasm, Satisfaction and Pain. An individual score was calculated for each sexual domain and an FSFI total score (sum of the weighted individual scores) was obtained for each patient. A cut-off value of 22.5 was used to classify patients as having sexual dysfunction or not (Brook Levis et al). Psychological, Functional and Quality of Life aspects were evaluated through the Hospital Anxiety and Depression Scale (HADS), Health Assessment Questionnaire (HAQ) and Short Form 36 (SF-36), respectively.
Statistical analysis was performed through SPSS. Comparison between groups was assessed through Mann-Whytney test or Chi 2 test, as adequate. p values <0.05 were considered significant in all statistical analyses.
Results. A total of 36 SSc women were included. Mean age was 58.8±11.1 years (mean ± SD) and 80.6% presented the limited disease subtype. 91.7% had a partner and 55.6% were sexually active. Among the sexually active patients, 55% had sexual dysfunction (FSFI total score <22.5). Desire was the most affected domain (mean Desire score of 1.691±0.647 and 3.467±0.88, in patients with and without sexual dysfunction, respectively). Mean Body Mass Index (BMI) was significantly higher in women with sexual dysfunction (28.04±4.626 vs 23.23±2.473; p=0.016). Higher anxiety levels were present in patients with sexual dysfunction (mean HADS-anxiety subscale of 10.73±2.054 vs 8.56±2.128; p=0.031,), although depression levels (HADS-depression subscale), functional disability (HAQ) and quality of life (SF-36) were similar in both groups. No differences were observed in sexual function according to SSc disease subtype.
Conclusion. The majority of the sexually active SSc women suffered of sexual dysfunction and this was related with higher anxiety and BMI levels, which poses additional questions in the treatment of these patients. Further research to investigate sexual dysfunction among these patients is needed.

PS72

THE VASCULAR HYPOTHESIS OF FEMALE AND MALE SEXUAL DYSFUNCTION

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To investigate the clitoral blood flow in systemic sclerosis (SSc) women and the flow inside cavernous arteries in SSc men. Doppler indices [peak systolic velocity (PSV), end diastolic velocity (EDV), the resistive index (RI), pulsatile (PI) indices and S/D (systolic/diastolic) ratio] were measured using an Aplio Ultrasound System SSA-790 (Tokio, Japan) equipped with convex 7.5 MHz probe. In SSc women Doppler indices of clitoral artery were measured at baseline, conversely in SSc men Doppler indices of cavernous arteries were measured at the peno-scrotal junction before and after pharmacostimulation with 20 mcg prostaglandin E1. Nailfold videocapillaroscopy (NVC) was performed by an optical probe videocapillaroscopy equipped with magnification 200 x contact lens and connected to image analysis software (Pinnacle Studio Version 8, Pinnacle Systems, Mountain View, California). The nailfold (distal row) of the second, third, fourth and fifth finger was examined in each patient.
Twenty women [median age 37 (25-45) years] and 20 men [median age 44 (21-58) years] fulfilling the American College of Rheumatology preliminary criteria for the classification of SSc were enrolled. The Female Sexual Function Index (FSFI) and International Index of Erectile Function-5 (IIEF-5) were used to assess sexual function in women and men, respectively. FSFI was reduced in 6 (30%) of 20 SSc women and IIEF-5 was reduced in 16 (80%) of 20 SSc men.
Eight women have an early capillaroscopic pattern, 6 have an active capillaroscopic pattern and 6 have a late capillaroscopic pattern. No significant differences of PSV and EDV were observed in the three capillaroscopic patterns. Conversely, PI, RI and S/D ratio were significantly different in the three capillaroscopic patterns. PI (p<0,01), RI (p<0,001) and S/D ratio (p<0,01) increased with progression of capillaroscopic damage.
Also in SSc men Doppler indices of cavernous arteries were different in three capilaroscopic groups. PSV (p<0,001) decreased and EDV (p<0,001) increased with progression of capillaroscopic damage. No significant differences of RI (p>0,05) were observed in three capillaroscopic groups.
We can conclude that artery inflow of clitoral and cavernous arteries is reduced in the vast majority of SSc women and men. The artery inflow decreased with progression of capillaroscopic damage.

PS73

IMPRESS 2 (INTERNATIONAL MULTICENTRIC PROSPECTIVE STUDY ON PREGNANCY IN SYSTEMIC SCLEROSIS). PROSPECTIVE, CASE-CONTROL STUDY OF PREGNANCY IN SYSTEMIC SCLEROSIS

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Background. Systemic Sclerosis (SSc) has its usual onset in the mid-forties, but it's not unusual to find SSc women wanting a child, especially nowadays where a great number of women delay pregnancy. Data on pregnancy in SSc are limited. We recently published a large retrospective study: IMPRESS (Italian Multicentric study on PREgnancy in Systemic Sclerosis), partially supported by Italian patients associations, that studied 99 SSc women and their 109 pregnancies, admitted in 25 Italian centers within the years 2000-2011, compared with a general obstetric population (GOP). In SSc women preterm deliveries (25% vs. 12%) and severe preterm deliveries (<34 weeks) (10% vs. 5%), intrauterine growth restriction (IUGR, 6% vs. 1%) and very-low-birth-weight babies (5% vs. 1%) were significantly more frequent than in the GOP. Multivariable analysis found that corticosteroid use was associated with preterm deliveries, while folic acid and anti-Scl70+ was protective. The disease remained stable in most SSc patients, but there were four cases of progression within one year from delivery.
Aim of the study. to plan a new fully prospective study: IMPRESS 2 (International Multicentric PRospective Study on PREgnancy in Systemic Sclerosis).
Patients and methods. we're planning a fully prospective, case-control study of 3 groups of people, enrolled at an International level: 1. 100 pregnant SSc patients, 2. 200 non-pregnant matched SSc women, 3. 200 healthy pregnant women. Their children will be studied at birth and at 1 and 3 years of age. IMPRESS 2 study will prospectively investigate disease activity of SSc during and after pregnancy, pregnancy complications and outcome in patients with SSc, children outcome at 1 and possibly 3 years, and the modern incidence of renal crisis, severe cardiac involvement and pulmonary hypertension in women with SSc, both pregnant and non-pregnant. Several ethical committees of the participating centres have approved the study, and enrolment is started: 14 pregnancies worldwide are currently ongoing.
Expected results and Conclusion. IMPRESS 2 will answer to the following important questions. 1. are complications of SSc more frequent during pregnancy than in the non-pregnant state? 2. Which is the current incidence of renal crisis, cardiac involvement, and pulmonary hypertension in scleroderma women, both pregnant and non-pregnant? 3. Is folic acid use protective for prematurity? 4. Are some autoantibodies protective for prematurity? 5.Which is the impact of prematurity on children development? Which is their IQ at 3 years? These data will be extremely important for counseling fertile SSc women contemplating a pregnancy.

Poster Tour 12: *Therapy*

PS74

ALLOGENIC SKIN GRAFTING FOR SYSTEMIC SCLEROSIS ULCERS: PRELIMINARY DATA OF AN ITALIAN COHORT

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Backgroud. Systemic sclerosis (SSc) is a systemic autoimmune disease of unknown etiology. Digital ulcers are common in patients with SSc with a prevalence around 30% while nondigital ulcers in are estimated at 4%. Both ulcers can cause severe pain and morbidity. Reconstructive surgery for hard-to-heal ulcers can be performed using preserved cadaver skin (allograft). This technique has been used both in burns and in chronic leg wounds by reducing pain, accelerating healing and minimizing scarring. The aim of this study was to assess the effect of allograft in a cohort of SSc patients with chronic ulcers.
Methods. From January 2006 to December 2012 consecutive SSc subjects affected by chronic ulcer (refractory to conventional treatment) referred to our vascular surgery department to perform allogenic skin grafting were enrolled. Data were retrospectively retrieved from clinical charts. Diagnosis of SSc was established using ACR criteria (1980). The primary outcome was to assess effectiveness in terms of pain reduction, evaluated using a visual analogue scale (VAS)and tolerability (rate of infection).
Results. A total of 43 SSc patients (5 male, 38 female) were treated using allogenic skin grafting. The mean age at the time of intervention was 60.8 years (min 39 – max 83). The ulcers were localized in the following areas: 34 lower extremities (10 digital), 8 upper extremities (3 digital), 1 both upper and lower digital ulcers. The mean ulcer duration was 27 months (min 2, max 140). Other risk factors for ulcers development recorded was:venous insufficiency (13 patients), arterial hypertension (17 patients), diabetes (3 patients), hypercholesterolemia (5 patients), obesity (1 patient).
The VAS for pain reduced by 84%: before the mean VAS value was 7.55 (min 4 – max 10) and immediately after the procedure was 1.18 (min 0 – max 5) – $p<0.001$. No serious side effects was recorded after the procedure. All patients healed completely, but 37 % had an ulcer recurrence in the same location during the subsequent year. No patient presented an infection in the grafting area during the first 4 weeks after the surgery.
Conclusion. The use of allogenic skin grafting may be a safe and effective treatment for SSc chronic ulcers. This procedure seems to favour wound healing and significantly reduces pain as compared to conservative dressing. Further studies and randomized controlled trials are needed to identify prognostic factors of response to allografts and to help the selection of patients most suitable for the procedure.

PS75

AUTOLOGOUS FAT TRANSFER FOR DIGITAL ULCERS TREATMENT IN SYSTEMIC SCLEROSIS

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Objective. Digital ulcers (DUs) occur in up to 50% of patients with Systemic Sclerosis (SSc). DUs are painful, recurring and lead to functional disability. Management of DUs includes pharmacologic and local therapy: the healing is slow and the ulcer can become infected or evolve to gangrene. Autologous fat grafting (AFG) is a technique used in reconstructive surgery to promote repair of soft tissues. We used AFG to treat DUs refractory to conventional treatment to enhance healing.
Methods. We treated 9 SSc patients with 16 DUs. All were treated with iv Iloprost: 8 patients with CCB (calcium channel blocker), 7 with low dose aspirin, 2 with sildenafil and 4 with bosentan to prevent recurrence. The purified fat tissue was injected on the border of larger ulcers or at the finger base of smaller DUs. The AFG was done from 2 to 8 months since the ulcer onset.
Results. No improvement was observed in 3 pts. The outcome was positive with complete healing in 10 DUs and size reduction > 50% in 2, in 8 to 12 weeks. In all but three patients the pain improved allowing a reduction of analgesics.
Conclusions. The AFG was able to hasten ulcer healing and to reduce pain and the need of pharmacological therapy in the majority of the cases. The lack of efficacy on healing and pain was observed when the ulcers were long-lasting and with concurrent atherosclerotic macroangiopathy, especially those located on legs. Furthermore in a single patient the AFG was effective on the digital ulcer whereas the outcome of the ulcer of the heel was very poor.

PS76

LUNG TRANSPLANTATION IN SISTEMIC SCLEROSIS: EXPERIENCE IN A SPANISH CENTER

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Objectives. To describe the clinical features, evolution, complications and survival of patients with Systemic Sclerosis (SSc) who received lung transplantation.
Methods. Six patients with SSc that underwent lung transplantation between May 2005 and July 2012 were included. Data were obtained from review of medical records and databases. Follow-up was continued until July 2013.
Results. All patients were caucasian. Four (66%) were women with a mean age of 45±8 years at the transplantation moment. Distribution by SSc subset according to the Le Roy and Medsger's criteria was: 4 limited and 2 diffuse. All patients had Raynaud's phenomenon and mild to moderate esophageal involvement; 5 musculoskeletal and heart involvement; 3 digital ulcers and pulmonary arterial hypertension (PAH).
Lung transplantation was carried out due to: interstitial lung disease (ILD) in 3 patients, ILD associated to PAH in 2, and 1 to PAH. Five lung transplants were bilateral and one unilateral. Initial complications were: gastroparesia in 3 patients, diaphragmatic palsy in 1, and acute cellular rejection in 2. Two individuals showed no early complications. Late complications were: bronchial stenosis in 2 patients, bronchiolitis obliterans syndrome in 2, and restrictive allograft syndrome in 1. All patients were immunosupressed with tacrolimus, mycophenolate mofetil and corticosteroids.
Median survival was 83% at one year and 80% at two years. Deaths were due to respiratory infections in two patients (39 and 54 months after transplantation) and lung adenocarcinoma in one (7 months after transplantation).
Conclusions. Lung transplantation is an effective treatment for advanced ILD and/or PAH associated to SSc patients. Bilateral lung transplantation was the most common procedure. In our series, infectious complications were the leading cause of death. Mortality at one and two years was similar to that described in the literature for other lung transplantation indications. More studies are needed to assess long term effectiveness of this treatment.

PS77

LONG TERM EFFICACY OF PERIORAL AUTOLOGOUS FAT TRANSPLANTATION ON SCLERODERMA SKIN FIBROSIS: A CONTROLLED STUDY VERSUS HYALURONIC ACID FILLER

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Autologous fat tissue grafting (AFTG) has been successfully used in the treatment of different sclerotic conditions, including scleroderma.
We evaluated in patients with SSc who complained of a reduced mouth opening, the long-term efficacy, safety and durability of AFTG of the lips in improving mouth opening in comparison with hyaluronic acid (HA) filler. We also investigated whether these procedures may induce some changes in the microvascular architecture and dermal structure of the treated skin area.
Materials and Methods. We studied 25 patients with dcSSc, (median age 35+15 yrs, disease duration 11+8years): 15 were treated by topical perioral AFTG according to Coleman technique and 10 by HA filler. Baseline and after treatment (at months 3, 6, and 12) mouth opening changes were assessed by measuring inter-incisal distance and oral perimeter, skin hardness was tested by digital durometer. Pre- and post-treatment modifications of microvascular architecture were assessed by counting capillaries in the inferior lip videocapillaroscopy (VC) images. Similarly, histological sections of perioral skin biopsy were examined at baseline and 3 months to evaluate dermo-epidermic junction (DEJ), the collagen content (by Masson's Trichrome staining) and microvessel density (MVD) (by anti-CD34/CD31staining).
Results. 3 months after treatment both the inter-incisal distance and oral perimeter significantly increased (p<0.001), and durometer scores were significantly decreased in comparison to the baseline evaluation (p=0.03). At the same time, a significant skin neovascularization became evident, both considering the VC images (p<0.001) and MVD scores in IH sections (p<0.0001). Finally, some skin histological aspects also improved, as shown by the significant changes in DEJ flattening scores (p<0.0001) and collagen content with less abnormal and denser collagen bundles. At 6 and 12 months, despite the disappearance of filling effect, both the functional improvement in mouth opening and the increased number of capillaries were maintained. No effect either on the mouth opening, VC images and skin histological aspects was observed in SSc patients treated by HA filler.
Conclusions. The present study shows that, in patients with SSc, AFTG can improve mouth opening, induce a neovascularization, and partially restore the skin structure. All these effects were confirmed in the long-term observation. The lack of functional and biological effects in the control group treated by HA filler, suggests that the observed therapeutic effect of lipostructure may be specifically ascribed to the on site transplantation of fat tissue. Our study may open new perspectives for the local and general therapeutic approach to SSc.

PS78

NEW FAT-DERIVED PRODUCTS FOR TREATING INDUCED-SKIN LESIONS OF SCLERODERMA IN NUDE MICE

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Scleroderma is an auto-immune disease characterized by an excessive fibrosis of the skin. We previously validated a murine model of scleroderma and showed an antifibrotic and a proangiogenic effect of fat microinjection (MF). Fat is harvested with a 14 gauge , 2mm cannula and reinjection is performed with a 21 gauge cannula. In addition to the MF, we purify the stromal vascular fraction (SVF) of adipose tissue and platelet-rich plasma (PRP) from blood. We evaluated and compared the efficacy of MF, SVF, PRP, and mixtures of these products: MF + SVF and MF + PRP, in the murine model of skin-induced lesions of scleroderma. This project was divided in three parts: Induction of skin sclerosis in nude mice by daily subcutaneous injections of bleomycin (BLM) during 4 weeks. Preparation and subcutaneous injections of the different cell therapy products of human origine. Skin biopsies 8 weeks post-injections. 66 nude mice were used. Fat was harvested from the abdomen, to obtain MF and SVF, peripheral whole-blood was taken ta prepare PRP. We injected 0.5 cc of the different cell therapy products containing respectively: 131,000 cells injected/mouse for the SVF and 0.64 million of platelets injected/mouse for PRP derived products. BLM skin-induced lesions were checked by histological analyses in control mice. BLM-treatment induced a 21.74% increase of the dermis thickness, a 40.28% increase of the epidermis thickness *i.e.* a 23.74% increase of the total skin thickness. Time didn't affect skin-induced lesions of scleroderma and injections of the control solutions (chloride sodium or ringer lactate) didn't reverse skin sclerosis. This work has demonstrated the effectiveness of these different biotherapies on skin-induced lesions of scleroderma. MF, MF + SVF and MF + PRP completely reversed while SVF and PRP partially corrected skin sclerosis. A 13.7% decrease of the dermis thickness was observed with SVF, and a 20.7% decrease was observed with the PRP. Products containing MF were still present 8 weeks post-injections, suggested the long-term potential effects of the MF. The number of visible vessels observed in the deep dermis was significantly increased in SVF or MF + SVF conditions, compared to others, showing the expecting SVF proangiogenic effects. We highlighted the interest of mixtures MF + SVF and MF + PRP compared to the MF, SVF and PRP separately for their regenerative and proangiogenic properties. These effects on the sclerotic skin should have potential clinical applications in the treatment of the SSC human disease.

PS79

THE USE OF ADIPOSE-DERIVED REGENERATIVE CELLS (ADRCS) IN THE TREATMENT OF SCLERODERMA OF THE HANDS: A PROSPECTIVE TRIAL

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Introduction. Hand disease in Systemic Sclerosis can be complicated by acrocyanosis, digital ischemia, ulcers and digital retraction which lead to functional disability, pain, and a significant impairment of the quality of life. Currents treatments are modestly effective. The safety, feasibility, functional and trophic effects of the injection of stromal vascular fraction (SVF) from adipose tissue in the fingers of patients with SSc were evaluated.
Patients and Methods. 12 patients with scleroderma who had undergone many treatment failures and expected an improvement of their hand disability were included, after consent and verification of the inclusion / non-inclusion criteria. All had a Cochin hand function disability Scale >20/90. The trial was granted a favorable opinion by the Ethical Committee and the French Health Products Safety (ANSM).
120 grams of fat were harvested from the abdominal region by liposuction under local anesthesia and immediately supported by the cell treatment unit. 5 ml of FVS were extracted with the Celution® 800/CRS (Cytori Therapeutics, Inc, USA) medical device. 1 ml was reinjected in the fingers under neuroleptic analgesia, using a 25-gauge cannula (0.5 mm), in the lateral areas of the proximal interphalangeal regions in the long fingers and in the metacarpophalangeal region in the thumbs. The injection was performed 2 hours after harvesting and quantification of the cell product. The average dose of cells injected per finger was 3.7 106. Clinical monitoring was programmed at one, seven, twenty-one days, two and six months.
Results. Mean age was 54.5±10.3 years, 7 patients had a cutaneous limited scleroderma and 12 had Raynaud's syndrome which appeared at 14.3±7.7 years (range 5-34) before. Duration of scleroderma was 9.9±7 years (range 2-24). Rodnan score was 14±9.7 (range 3-32). The ulnar and radial arteries were patent by Doppler ultrasound. No infectious or ischemic complications were observed. No serious adverse events were reported. Results from several tests showed a significant improvement (p<0,001): Cochin hand functional disability scale; pain in hands evaluated with the visual analogic pain scale. Raynaud's syndrome; SSc-HAQ. Hand mobility test (HAMIS) and Rodnan score focused on hand were improved.
Conclusion. This study demonstrates the feasibility and tolerability of injecting autologous FVS in the fingers. An improvement was observed in hand functions, the intensity of pain in the fingers, Raynaud's syndrome and quality of life.

PS80

NO CORRELATION OF CD4+ LYMPHOPENIA AND CLINICAL RESPONSE TO AUTOLOGOUS STEM CELL TRANSPLANTATION FOR SYSTEMIC SCLEROSIS

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Background. Autologous stem cell transplantation (aSCT) for systemic sclerosis (Ssc) has recently been proven effective. Nevertheless there are patients who respond to therapy very impressively and sustained and others who do not or relapse. Purpose of this study was to evaluate a possible correlation of long lasting lymphopenia and response to treatment.
Methods. CD4+ lymphocytes of 32 (20 male and 12 female) patients who underwent aSCT in Tuebingen were evaluated. Our treatment regimen consists of cyclophosphamide (CYC) + granulocyte stimulating factor (GCSF) for mobilization; CD34+ selection and CYC + antithymocyteglobuline (ATG) or CYC + ATG + thiotepa (n=6) for conditioning (n=26). Response to treatment was defined as improvement of modified rodnan skinscore (mRSS) >25%. As a relapse we counted patients with any worsening in thoracal CT scan or >25% in mRSS. CD4+ lymphocytes were counted using immunophenotyping by fluorescence activated cell sorting.
Results. Twenty-seven (84%) of the patients responded to treatment whereas 5 patients (15%) showed no improvement. Six patients (19%) relapsed and 21 (66%) achieved an ongoing treatment success. We found a long lasting lymphopenia in most of the patients but no correlation between sustained response and lymphopenia, even more those patients with good response recovered rather earlier.
Conclusion. CD4+ lymphopenia is not the key mechanism underlying the ongoing response to aSCT for patients with Ssc.

PS81

INTEREST OF MICRO REINJECTION OF AUTOLOGOUS ADIPOSE TISSUE IN THE FACE OF PATIENTS WITH SYSTEMIC SCLEROSIS

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Orofacial manifestations of systemic sclerosis (SSc), found in over 90% of cases, are responsible for functional disability and significant aesthetic discomfort. The score Mouth Handicap in Systemic Sclerosis (MHISS) assesses specifically disability involving the mouth and the face. It explains for over 36% of the total disability related to SSc.
SSc presents with a wide range of orofacial manifestations including perioral skin fibrosis, perioral wrinkles, limited mouth opening, sicca syndrome and temporo-mandibular pain syndrome.
In the absence of standard treatment, we propose an open study analyzing the functional and aesthetic effects of micro reinjection of autologous fat in the face of SSc patients.
Adipose tissue has been used for more than one century for its volumizing and trophic properties. Indeed, it contains stromal vascular fraction rich in multipotent mesenchymal stem cells called Adipose-Derived Stem Cells (ADSCs).
Material and Methods. This prospective single-center opened pilot study includes 13 patients with SSc according to the American College of Rheumatology criteria and the Leroy & Medsger criteria for SSc. All patients wish for a therapeutic care of their face. They present a MHISS score greater than 20 and a mouth opening less than 55 millimeters. They have no anticoagulant medication or daily corticosteroid greater than 20mg per day, their BMI exceed 17. Micro fat grafting is a minimally invasive procedure performed under local anesthesia. Fat tissue is harvested using a 14 gauge or 2mm cannula. Then it is refined as described by SR Coleman. 10 to 25cc of this product is transferred through a 21 gauge or 0.8mm cannula in four points of the face.
Patients are assessed at baseline, three and six months after surgery.
Results. The expected outcome is improvement of the MHISS score at least 5 points over 48.
The results of secondary endpoints will evaluate clinical data (Health Assessment Questionnaire adapted to scleroderma, painful facial syndrome, sicca syndrome, Rodnan score for the face, tolerance) and paraclinical aspects (cutometry data and 3D photography).
Conclusion. The injection of autologous adipose tissue has shown efficacy in the treatment of limited forms of scleroderma . This study aims to evaluate the effectiveness of this non-invasive procedure in treatment of orofacial manifestations in SSc. It could offer a safe and non-invasive way to improve patients' quality of life.

PS82

HUMAN ADIPOSE-DERIVED STROMAL CELLS FOR CELL-BASED THERAPIES IN THE TREATMENT OF CUTANEOUS MANIFESTATIONS IN PATIENTS AFFECTED BY SYSTEMIC SCLEROSIS (SSC)

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The present study was designed to evaluate the clinical outcome of cell-based therapy with cultured adipose derived stromal cells (ASCs) for the treatment of cutaneous manifestations in patients affected by systemic sclerosis (SSc). ASCs have an extraordinary developmental plasticity, including the ability to undergo multilineage differentiation and self-renewal. Moreover, ASCs can be easily harvested from small volumes of liposuction aspirate, showing great in vitro viability and proliferation rate. Here we isolated, characterized, and expanded ASCs, assessing both their mesenchymal origin and their capability to differentiate towards the adipogenic, osteogenic, and chondrogenic lineage. We developed an effective method for ASCs transplantation into sclerodermic patients by means of a hyaluronic acid (HA) solution, which allowed us to achieve precise structural modifications. ASCs were isolated from subcutaneous adipose tissue of six sclerodermic patients and cultured in a chemical-defined medium before autologous transplantation to restore skin sequelae. The results indicated that transplantation of a combination of ASCs in HA solution determined a significant improvement in tightening of the skin without complications such as anechoic areas, fat necrosis, or infections, thus suggesting that ASCs are a potentially valuable source of cells for to improve dermal repair in rare diseases such as SSc and generally in skin disorders.

Poster Tours – *Basic*

Poster Tour 13: *Pathogenesis*

PS83

ANGIOTENSIN RECEPTOR TYPE 1 AND ENDOTHELIN RECEPTOR TYPE A ON IMMUNE CELLSMEDIATE MIGRATION AND THE EXPRESSION OF IL-8 AND CCL18 WHEN STIMULATED BY AUTOANTIBODIES FROM SYSTEMIC SCLEROSIS PATIENTS

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Background. Agonistic autoantibodies against the angiotensin II receptor type 1 (AT1R) and the endothelin receptor type A (ETAR) have been identified in patients suffering from systemic sclerosis (SSc). Here we examined the expression of AT1R and ETAR in human immune cells and pathological effects mediated through these receptors by corresponding autoantibodies (Aabs).
Methods. AT1R and ETAR protein expression on peripheral blood mononuclear cells (PBMCs) from healthy individuals and SSc patients was analyzed using flow cytometry, and mRNA expression was examined by real-time PCR in PBMCs from healthy donors. In addition, PBMCs from healthy donors were stimulated in vitro with affinity-purified immunoglobulin G (IgG) fractions from SSc patients positive for AT1R- and ETAR-Aabs, and with IgG from healthy donors serving as control. Alterations in chemotactic motility and cytokine secretion were analyzed using chemotaxis assays and ELISA, respectively. Results were correlated with characteristics/clinical findings of the IgG donors.
Results. Both AT1R and ETAR were expressed on human peripheral lymphocytes and monocytes. Protein expression of both receptors was decreased in SSc patients when compared to healthy donors and correlated negatively with disease duration. In addition, IgG fractions of SSc patients induced T cell migration in an anti-AT1R and anti-ETAR Aab level-dependent manner. Moreover, IgG of SSc patients was capable of stimulating PBMCs to produce more IL-8 and CCL18 than IgG of healthy donors. All effects could be significantly abrogated by the application of selective AT1R and ETAR antagonists. Statistical analysis revealed a negative correlation between SSc IgG-induced IL-8 concentrations and disease duration, between SSc IgG-induced CCL18 concentrations and time since onset of lung fibrosis as well as an association of CCL18 concentrations with vascular complications of the corresponding SSc IgG donors.
Conclusion. We demonstrated the expression of both, AT1R and ETAR, on human peripheral T cells, B cells and monocytes, and found a decreased receptor expression on cells from SSc patients suggesting downregulation due to chronic activation. The inflammatory and profibrotic effects upon Aab stimulation in vitro, and their associations with clinical findings indicate a role for autoantibody-mediated activation of immune cells mediated through the AT1R and ETAR in the pathogenesis or even the onset of the disease.

PS84

ANTI-AT1R AND ANTI-ETAR AUTOANTIBODIES FROM PATIENTS WITH SSCANDTHEIRAGONISTIC EFFECTS

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Background. Functional autoantibodies to angiotensin II type 1 receptor (AT1R) and endothelin 1 type A receptor (ETAR) are found in elevated levels in systemic sclerosis (SSc) and show association to increased risk of SSc-related manifestations and reduced cumulative survival. Biologic effects of these autoantibodies (anti-AT1R and anti-ETAR autoantibodies) have been demonstrated in vitro. Here, the functional effects were studied in vivo using animal models.