Methods: SLS I randomized 158 SSc-ILD patients to 12 months of cyclophosphamide (CYC) vs. placebo. SLS II randomized 142 SSc-ILD patients to 12 months of CYC, followed by 12 months of placebo vs. 24 months of mycophenolate (MMF). QILD-WL scores were calculated at baseline and 12 months (SLS I) and 24 months (SLS II). Participants were followed for up to 12 (SLS I) and 8 years (SLS II). Using landmark survival analysis, Kaplan Meier curves were generated to compare survival between participants who had worse QILD-WL scores ($\geq 2\%$ increase) and those who had stable/improved QILD-WL scores ($< 2\%$ increase). Cox proportional hazards models were created to determine whether the change in QILD-WL scores predicted survival after controlling other variables found to affect survival in these cohorts.

Results: Among all the SLS I and II participants, 82 and 90 had follow up HRCT scans, respectively, and were included in these analyses. SLS I participants with an increase in QILD-WL scores of $\geq 2\%$ at 12 months had significantly worse long-term survival ($P = 0.01$; Figure). Similarly, SLS II participants with an increase in QILD-WL scores of $\geq 2\%$ at 24 months had significantly worse long-term survival ($P = 0.019$; Figure). After adjusting for baseline FVC, age, and modified Rodnan skin score (mRSS), an increase in QILD-WL scores of $\geq 2\%$ remained associated with worse long-term survival in SLS I ($trend: P = 0.089$) and SLS II ($P = 0.014$).

Conclusion: Progression of the radiographic extent of ILD of $\geq 2\%$ was associated with worse long-term survival in two independent SSc cohorts with extensive long-term follow up. The findings provide compelling evidence that short-term changes in the radiographic extent of ILD may serve as a surrogate endpoint for mortality in patients with SSc.

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OP0268

TREATMENT STATUS AFFECTS HOW PULMONARY BIOMARKERS PREDICT PROGRESSION OF SYSTEMIC SCLEROSIS-RELATED INTERSTITIAL LUNG DISEASE

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Background: The course of interstitial lung disease (ILD) varies considerably in patients with systemic sclerosis (SSc), and no biomarkers have been found to

consistently predict ILD progression in this population. Treatment may affect how a candidate biomarker correlates with improvement/worsening of SSc-ILD. We hypothesized that specific proteins recovered from bronchoalveolar lavage (BAL) would differentially predict progression of SSc-ILD based on whether a patient was receiving ILD therapy.

Objectives: (1) To assess the relationship between 68 unique BAL proteins measured in participants of Scleroderma Lung Study (SLS) I¹ and changes in radiographic extent of SSc-ILD; (2) To determine if treatment affects whether a specific protein predicts improvement or worsening of SSc-ILD.

Methods: Bronchoscopy was performed on 144 of the 158 participants in SLS I (Cyclophosphamide [CYC] vs. placebo) with 103 BAL samples available for analysis. BAL was lyophilized, concentrated 10X and used in a multiplex protein analysis of 68 distinct cytokines, chemokines and growth factors. Quantitative imaging analysis (QIA) was used to calculate the extent of radiographic fibrosis (QLF) in the whole lung using HRCT of the chest at baseline and 12 months. Multivariable linear regression models were created to determine the key BAL proteins associated with change in QLF scores using a backward selection process adjusting for treatment arm and ILD severity. The bootstrap procedure was employed for internal validation.

Results: A number of BAL proteins were significantly associated with change in QLF scores at 12 months; however, the directionality of these associations was often based on the presence/absence of treatment. For example, increased levels of granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin (IL)-1, monocyte chemoattractant protein (MCP)-3, chemokine ligand (CCL)-5, transforming growth factor (TGF)- β , hepatocyte growth factor (HGF), stem cell factor (SCF), IL-4, TGF- α , were associated with worse QLF scores in patients who received placebo; whereas, increased levels of these same proteins were associated with improved QLF scores in patients who received CYC (Figure). Increased levels of Fractalkine were associated with worse in QLF scores, and increased levels of IL-7 were associated with improved QLF scores, regardless of treatment arm. In the multivariable model adjusting for treatment arm and baseline severity of ILD, IL-1, MCP-3, surfactant protein C, IL-7, and CCL-5 were independently associated with change in QLF scores.

Figure 1. Example of a specific BAL protein (GM-CSF) that predicts worse QLF scores in patients receiving placebo (Group B, Red dotted line) and improved QLF scores in patients receiving CYC (Group A, Blue solid line). Shaded areas represent 95% confidence intervals.

Conclusion: Proteins that mediate both inflammation and fibrosis differentially affected progression of SSc-ILD based on treatment status. Higher levels of certain proteins predicted worsening of ILD in patients receiving placebo, but improvement in patients receiving CYC. Measuring these proteins could help to identify patients who: (1) are at risk for ILD progression, and (2) may preferentially benefit from treatment with immunosuppression.

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OP0269

A COMBINED CLINICAL AND BIOMARKER ALGORITHM TO PREDICT FVC DECLINE IN SYSTEMIC SCLEROSIS ASSOCIATED INTERSTITIAL LUNG DISEASE: RESULTS FROM AN INTERNATIONAL MULTICENTRE OBSERVATIONAL COHORT

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Background: Interstitial lung disease (ILD) is the leading cause of mortality in patients with Systemic Sclerosis (SSc). Forced Vital Capacity (FVC) is a major indicator of severity in SSc ILD. The ELF serum test and its constituent biomarkers (HA, PIINP and TIMP-1) have shown to correlate with FVC in two large, independent multicentre cohorts of 457 patients, but also showed a correlation with age.

Objectives: Here we aimed to investigate the relationship of the ELF biomarkers and age in a large population of healthy controls and to identify a combined clinical and biomarkers model to stratify for risk of ILD progression in a multicentre longitudinal cohort of patients with SSc.

Methods: ELF score was measured in sera from 925 healthy controls in one centre and 869 longitudinal samples from 254 SSc patients from 6 centres across 4 European countries. Clinical data were recorded according to EUSTAR Minimal Essential dataset. FVC% change over time was estimated by Mixed-effects modelling. Patients were then divided in two groups: progressors, with a %FVC drop > 3%/year (according to published MCID) and a group of patients with stable or improving FVC. Lasso penalised regression was carried out with biomarkers and the available clinical and demographic variables at patient's first visit as potential predictors. The resulting linear predictor was used to derive two thresholds, one for optimal sensitivity (rule-out) and one for optimal specificity (rule-in). Patients within thresholds were further selected according to the ratio of TIMP-1: PIINP (Figure 1).

Results: HA was the only ELF biomarker that correlated significantly with age in the healthy control cohort. Therefore, we defined by linear regression a "residual HA" which accounted for age. TIMP1, PIINP and residual HA were then considered as distinct biomarkers in the analysis of the SSc cohort. 189 SSc patients with 785 time-points had complete datasets and were included in the analysis. Median follow up was 33 months (IQR 18-48). One-hundred and forty patients (74%) were classified as non progressors, 94 (50%) with no change or improving FVC and 46 (24%) with FVC drop <3% year. 49 patients (26%) were classed as progressors (drop of 3%/year or more in FVC, median slope -4.7%/year). Variable selection via Lasso penalised logistic regression resulted in a model with a c-index of 0.69 (95% CI: 0.60-0.78) and contained age, disease duration (from first non-Raynaud's symptom), residual HA, anti-centromere antibodies (ACA) status, previous diagnosis of ILD, joint synovitis and history of protein pump inhibitor use. A two-step process was developed using the linear predictor from the model and the ratio of TIMP-1 and PIINP (Figure 1). The stratification tool increased by nearly two-fold the ability to predict progressors in any 12 months interval (46 to 49% predictive value vs 26% probability) identifying an 82 to 91% negative predictive value for progression.

Conclusion: Building on the face and content validity of the biomarkers included in the ELF score, here we identify an easy to assess combined clinical and biomarker model to stratify patients for their risk of ILD progression. Despite its derivation from a large multicentre cohort, independent validation will determine the clinical value of Sclerosiscore as a stratification tool for risk of progression of SSc ILD.

Figure 1: Two-step process to stratify patients for risk of ILD progression
Patients with overall 24% risk of 3% yearly FVC drop are stratified by regression model in patients with 49% (rule in) vs 9% risk (rule out) in (Step 1). Patients in between thresholds of Step 1 are further stratified according to the biomarker ratio (TIMP1/PIINP) in the same risk categories.

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OP0270 LONG-TERM EFFICACY AND SAFETY OF BOSENTAN IN PATIENTS WITH DIGITAL ULCERS RELATED TO SYSTEMIC SCLEROSIS

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Background: Two pivotal studies, RAPIDS-1 and RAPIDS-2 revealed that bosentan reduces the development of new digital ulcers (DUs) in patients with systemic sclerosis (SSc). However data regarding the long-term use of this dual endothelin antagonist receptor in the treatment of DUs is scarce.

Objectives: The aim of the present study was to evaluate long term efficacy and safety profile of bosentan in patients with DUs related to SSc.

Methods: A prospective observational case-control study, conducted between 2014 and 2020 enrolled 65 SSc patients with ≥1 active DUs at baseline, who received bosentan therapy. Demographic and clinical features, including DUs incidence and patients subjective perception of DU pain and/or Raynaud's Phenomenon, were collected. Nailfold videocapillaroscopy was performed in all patients.

Results: The study included 51 females and 14 males, with a mean age of 52.6 years, 30 with diffuse subset, most of them with late scleroderma pattern (46/65). Number of DUs at baseline was 4.55 (±2.8), median duration of treatment was 25.95 (±19.4) months. Microangiopathy evolution score (MES) was 5.1 (2.19), visual analog scale (VAS) for DU was 77.9, VAS for Raynaud was 73.4.

Patients receiving bosentan had clinically significant reduction in the mean number of DU ($p<0.001$). The effect was most powerful for the first 6 months of treatment, but the improvement was sustained until 24 months' follow-up, when the mean DU number reached a plateau that was kept until end of study. 6 month and 24 month evaluations also revealed significant decrease in the VAS for DU ($p<0.05$) and in the VAS for Raynaud ($p<0.01$). Statistically significant difference was noted between bosentan-treated and the control group with respect to the decrease in the mean number of digital ulcers. ($p=0.005$).

There was a clear trend towards an improvement in MES score, between baseline and the next follow-up assessments ($p=0.003$). The difference was statistically significant when compared to control group, but only for the first 18 months of treatment ($p<0.001$).

14 patients (28.75%) discontinued bosentan therapy for administrative reasons. The median time among patients who interrupted the treatment was 6.9 months. An accelerated development of new DU was described 6 months after ($p=0.02$). Following commencement of bosentan, the mean number of DU has rapidly decreased ($p=0.008$). There was no significant difference between patients who temporarily discontinued bosentan for 6 or 12 months.

Bosentan was stopped due to lack of efficacy in 2 cases and due to side effects in 7 cases: 4 elevated liver enzymes, 1 severe thrombocytopenia, 1 dyspnea aggravation and low blood pressure.

Conclusion: The present data suggest that treatment with endothelin receptor antagonist bosentan was associated with a significant reduction in the mean number of DU in patients with SSc. The beneficial effect of bosentan persisted throughout the study but was most evident in the first 6 months of treatment. Statistical analysis showed a significant improvement of the microangiopathy evolution score from baseline to end of therapy. 14 patients had a high relapse rate due to potential rebound effect, 6 months after bosentan withdrawal. The drug was reintroduced successfully for 10 (70%) patients with a significant decrease in the number of DU.

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