with hypotonic oesophagus presented a reduced FVC ($84.63\% \pm 22.86\%$ vs $102.93 \pm 21.40\%$, $p < 0.0001$), TLC ($79.85\% \pm 19.62\%$ vs 95.29 ± 19.80 , $p < 0.0001$) and DLCO ($42.88\% \pm 20.00\%$ vs $59.89 \pm 20.78\%$, $p < 0.0001$) at baseline and to a faster deterioration of DLCO median values ($5.10\% \pm 20.61\%$ vs $-4.77 \pm 14.23\%$, $p = 0.012$) at follow-up. Patients with hypotonic oesophagus have an higher prevalence of diffuse skin disease and ongoing immunosuppressive treatment, but were comparable in term of age, sex, BMI, smoking habits, disease duration and prevalence of autoantibodies to the patients without this alteration.

Conclusions: The esophagogram is wide available, well tolerated and inexpensive tool to assess upper gastro-intestinal tract involvement and its abnormalities are associated to SSc-ILD severity. Because of a faster deterioration of lung function is associated to esophagogram abnormalities, a complete gastro-intestinal evaluation in ILD-SSc patients is mandatory.

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THU0405

THE ASSOCIATION BETWEEN BASELINE SERUM RESISTIN LEVELS AND THE DEVELOPMENT OF NEW DIGITAL ULCERS IN PATIENTS AFFECTED BY SYSTEMIC SCLEROSIS

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Background: Resistin is a soluble factor produced by adipose tissue, implicated in the regulation of inflammatory processes and in microvascular damage.¹ When incubated with resistin, endothelial cells respond by a greater production of endothelin-1, a potent endothelium-derived vasoactive factor that engenders endothelial dysfunction (ED) in many cardiovascular and autoimmune diseases, such as Systemic Sclerosis (SSc).² SSc is a complex connective tissue disease, whose pathogenesis results from the variable interaction of three main processes: microvascular damage, autoimmunity-mediated inflammation and fibroblast activation.³ ED is at the base of the development of painful ischaemic events due to chronic hypoxia, namely digital ulcers (DUs),⁴ considered a prognostic marker of disease severity.⁵

Objectives: To evaluate the association between baseline serum resistin levels and the development of new DUs in a cohort of patients with SSc.

Methods: We conducted a one-year prospective cohort study. Patients with SSc and healthy controls (HC) were consecutively enrolled. Baseline serum resistin was assessed by commercial ELISA kit. The development of new DUs was prospectively evaluated during the follow-up after the cross-sectional point in which the resistin levels were measured.

Results: We enrolled 70 SSc patients and 26 HC matched by gender and vital parameters. Mean basal resistin levels were increased in SSc patients compared to HC (6.58 ± 5.48 vs 2.56 ± 0.95 , $p = 0.0004$). In SSc group, resistin was higher among patients with active DUs ($p = 0.0007$), infected DUs ($p = 0.0009$) and active pattern at nailfold videocapillaroscopy ($p = 0.01$). During one-year follow-up, 27 (38%) SSc patients presented new skin ulcers. Baseline resistin was increased in patients who developed new DUs (8.4 ± 6.4 vs 5.4 ± 4.5 , $p = 0.026$). In multiple logistic regression, the development of new DUs was associated to basal serum resistin concentration (OR 2.1, 95% CI 1.1–3.9), to the presence of active DUs at

baseline (OR 3.4, 95% CI 1.0–11.9), and to basal Disease Activity Score (DAI) according to European Scleroderma Study Group⁶ (OR 1.3, 95% CI 1.0–1.6). In proportional Cox regression, the time to new DUs was associated to basal resistin concentration (HR 1.7, 95% CI 1.1–2.8) and DAI (HR 1.2, 95% CI 1.0–1.4).

Conclusions: Serum resistin seems to be associated to the presence and to the development of DUs, suggesting a possible involvement in micro-vascular dysfunction in patients affected by SSc.

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THU0406

IV CYCLOPHOSPHAMIDE VS. RITUXIMAB FOR THE TREATMENT OF EARLY DIFFUSE SCLERODERMA LUNG DISEASE: OPEN LABEL, RANDOMISED, CONTROLLED TRIAL

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Background: Systemic sclerosis is characterised by fibrotic changes in the skin and lung, and the mainstay of treatment has been cyclophosphamide. B cell involvement suggests that rituximab may also be of therapeutic benefit. In this study, we compared the safety and efficacy of rituximab compared to cyclophosphamide in the treatment of skin and lung manifestations of systemic sclerosis.

Objectives: The aims of the study were to assess the efficacy and safety of IV Rituximab compared to IV cyclophosphamide in the primary therapy of systemic sclerosis, with particular emphasis on pulmonary and dermatological manifestations.

Methods: We randomly assigned 60 patients of systemic sclerosis, age 18–70 years with skin and lung involvement, to monthly pulses of cyclophosphamide 500 mg/sq. m or rituximab 1000 mg x 2 doses at 0, 15 days. Primary outcomes were forced vital capacity (FVC) percent predicted at six months. Secondary outcomes were: absolute change in litres (FVC-L) at six months; modified Rodnan Skin Scores at 6 months, six-minute walk test (6MWT), and Medsger's score

Results: The FVC (%mean $\pm$ SD) in Rituximab group improved from $61.30 (\pm 11.28)$ to $67.52 (\pm 13.59)$ while in Cyclophosphamide group, it declined from $59.25 (\pm 12.96)$ to $58.06 (\pm 11.23)$ at 6 months ($p = 0.003$). The change of FVC was $1.51 (\pm 0.45)$ L to $1.65 (\pm 0.47)$ L in Rituximab group compared to $1.42 (\pm 0.49)$ to $1.42 (\pm 0.46)$ L in Cyclophosphamide group. The mRSS changed from $21.77 (\pm 9.86)$ to $12.10 (\pm 10.14)$ in RTX group and $23.83 (\pm 9.28)$ to $18.33 (\pm 7.69)$ in Cyclophosphamide group after 6 months. Serious adverse events were more common in the cyclophosphamide group.

	Rituximab (n=30)			Cyclophosphamide (n=30)			Difference at 6 months Mean (95% CI)	p-value
	Baseline (mean (SD))	6 months (mean (SD))	p-value	Baseline (mean (SD))	6 months (mean (SD))	p-value		
Forced vital capacity (%)	61.30 (11.28)	67.52 (13.59)	0.002 ^a	59.25 (12.96)	58.06 (11.23)	0.496 ^a	9.46 (3.01 to 15.90)*	0.003 ^b
Forced vital capacity (L)	1.51 (0.45)	1.65 (0.47)	<0.001	1.42 (0.49)	1.42 (0.46)	0.356	0.23 (-0.013 to 0.47)**	0.091 ^b
Modified Rodnan Skin Score at baseline	21.77 (9.86)	12.10 (10.14)	<0.001	23.83 (9.28)	18.33 (7.69)	<0.001	-6.23 (-10.88 to -1.58)***	0.001 ^b
Medsger's Severity Scale	8.33 (3.04)	4.67 (2.35)	<0.001	9.60 (2.44)	5.96 (2.81)	<0.001	-1.30 (-2.64 to 0.04)#	0.036 ^b
6 min walking test (metres)	359.63 (65.95)	409.60 (69.29)	<0.001	335.90 (89.30)	349.14 (99.75)	0.428	60.46 (16.07 to 104.84)	0.001 ^b
Pulmonary hypertension present	4 (13%)	5 (16%)		5 (16%)	5 (16%)		##	

a Statistical comparison for FVC (%) before and after therapy for each group were done with paired-t test. For all other outcome variables same analysis was run with Wilcoxon signed rank test and reported p-values are 2-tailed only.

b Denoted comparison of outcome variables at 6 month between the two treatment groups i.e., rituximab versus cyclophosphamide. P-values were calculated by Mann-Whitney U test and reported p-values are 2-tailed only.

* $p = 0.005$ ** $p = 0.063$ *** $p = 0.01$ **** $p = 0.008$ # $p = 0.057$ ## $p = 1$

Conclusions: Rituximab is a safe and effective alternative to cyclophosphamide in the primary therapy of skin and lung manifestations of scleroderma.

Disclosure of Interest: None declared

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THU0407

EVALUATION OF SOLUBLE AND MEMBRANE HLA-G IN PATIENTS WITH SYSTEMIC SCLEROSIS AND ROLE OF THESE MOLECULES IN THE PATHOGENESIS OF THE DISEASE

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Background: Systemic sclerosis (SSc) is a complex disease characterised by immune abnormalities, vascular damage and fibrosis. Human leukocyte antigen-G (HLA-G) is a non-classic class I major histocompatibility complex (MHC) molecule expressed on different cell lineages in both physiological and pathological conditions and detectable in soluble forms (sHLA-G1 and HLA-G5 shed and secreted isoform, respectively). Several immunomodulatory functions have been attributed to both membrane-bound and soluble HLA-G molecules. HLA-G is expressed on extravillous cytotrophoblast, in placenta but also in a few normal tissues, solid tumours, transplanted organs and virally infected cells. Soluble form (sHLA-G) derives from shedding of cleaved surface isoforms (sHLA-G1) or secretion of soluble isoforms (HLA-G5). Immunosuppressive functions have been attributed to both membrane HLA-G (mHLA-G) and sHLA-G.

Objectives: The aims of the present study were: 1) to determine the serum levels of sHLA-G molecules in a cohort of SSc patients with the limited or diffuse form of the disease; 2) to correlate sHLA-G levels with TGF- β ; 3) to evaluate the expression of HLA-G in peripheral blood mononuclear cells (PBMC).

Methods: Thirtyfive patients (28 females/7 males, age 40–89 years) with diffuse SSc (dSSc, n. 12) or limited SSc (lSSc, n. 23) and 40 healthy sex and age matched controls were enrolled. Plasma sHLA-G, sHLA-G1 and HLA-G5 levels were determined by immunoenzymatic assays. mHLA-G expression in peripheral blood mononuclear cells (PBMC) was evaluated by flow cytometry.

Results: The plasma levels of sHLA-G were higher in SSc patients (444.27 ± 304.84 U/ml) compared to controls (16.74 ± 20.58 U/ml) ($p < 0.0001$). The plasma levels of TGF- β were higher in SSc patients (18937 ± 15217 pg/ml) compared to controls (11099 ± 6081 pg/ml; $p = 0.003$) and a significant correlation was found between TGF β and the plasma levels of total sHLA-G ($r: 0.65$; $p < 0.01$), sHLA-G1 ($r: 0.60$; $p = 0.003$) and HLA-G5 ($r: 0.47$; $p = 0.02$). The percentage of HLA-G-positive monocytes (0.98 ± 1.72), CD4+ (0.37 ± 0.68), CD8+ (2.05 ± 3.74) and CD4+CD8+double positive cells (14.53 ± 16.88) was higher in SSc patients than in controls (0.11 ± 0.08 , 0.01 ± 0.01 , 0.01 ± 0.01 and 0.39 ± 0.40 , respectively) ($p < 0.0001$). A high percentage of HLA-G+ cells (30.47 ± 26.75) was detectable on CD4^{dim}CD8^{high} cells from SSc patients only.

Conclusions: These data indicate that in SSc secretion and/or shedding of sHLA-G and mHLA-G are clearly elevated and involved in immune dysregulation.

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THU0408

CHARACTERISTICS OF MILD TO MODERATE LUNG DISEASE IN SYSTEMIC SCLEROSIS AND IMPACT OF SURVIVAL; DATA FROM THE POPULATION-BASED, NATIONWIDE NORWEGIAN COHORT

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Background: In systemic sclerosis (SSc) it is well-documented that severe interstitial lung disease (ILD), defined as an extent of lung fibrosis >20% on high resolution computed tomography (HRCT) is strongly associated with male gender, anti-topoisomerase antibody (ATA), diffuse cutaneous (dc) form of disease and decreased survival. Much less is, however, known about the disease characteristics and impact of less lung involvement. A possible explanation might be the selected nature of many hitherto investigated SSc cohorts. In an era with novel treatment options, and multiple ongoing clinical trials, it is important to gain natural history knowledge on the whole spectre of lung involvement in systemic sclerosis.

Objectives: Characterise the SSc patients with mild to moderate ILD, defined as 1%–10% extent of lung fibrosis on HRCT in the population based nationwide Norwegian SSc cohort and assess the impact of this ILD form on survival.

Methods: The Norwegian, nationwide SSc (Nor-SSc) study cohort included all adult SSc patients who were resident in Norway between 01.01.2000–01.01.2013 and met the classification criteria for SSc. Detailed electronic patient journal review was performed in all patients to assess demographic, clinical and ILD features at baseline. Pulmonary function tests (PFTs) and lung HRCT images were analysed and the extent of lung fibrosis was expressed as percentage of total lung volumes. We defined mild-moderate ILD as 1%–10% fibrosis on HRCT and severe disease as >20% fibrosis. Ground glass opacities, bronchiectasis and honeycombing were registered if present. Vital status and causes of deaths were available in all patients at study end (January 2018). Descriptive statistics and regression analysis were applied.

Results: The Nor-SSc cohort included 815 patients. Baseline lung HRCT images were available in 416 patients (51%), whereof 226 (54.3%) had signs compatible with ILD. Mild to moderate ILD, defined as 1%–10% lung fibrosis were present in 149 (65.9%), while 48 (21.2%) had extensive lung fibrosis defined as >20%. Patients with mild-moderate ILD were 55.2 years at SSc onset and characterised by female gender (81.9%) and limited cutaneous SSc (70.5%). Their antibody profile was dominated by anti-centromere Ab (ACA) in 48.3%, followed by anti-polymerase III, ATA, and anti-RNP, in 14.1%, 13.4% and 5.4%, respectively. The mean modified Rodnan skin score (mRSS) was 9.3 (9.3%), baseline FVC was 93.4% and DLCO 66.5%. Univariable associations of clinical characteristics and mild-moderate ILD are shown in figure 1. After a mean observation time of 8.2 years, 49 (32.9%) of patients with mild-moderate ILD had died. The 5- and 10 year survival was 76% and 62% compared to 83% and 76% in patients with no ILD ($p = 0.03$). In univariable cox regression analyses, mild-moderate ILD was associated with mortality (HR 1.6, 95% CI 1.03–2.40, $p = 0.034$).

Abstract THU0408 – Figure 1. Associations of clinical characteristics and mild-moderate ILD at baseline

Conclusions: In this population based, nationwide study, mild-moderate ILD was frequent and had a considerably impact on survival in SSc patients.

Disclosure of Interest: None declared

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