THU0402 DO WE HAVE GOOD INSTRUMENTS TO PREDICT MAJOR CARDIOVASCULAR EVENTS IN SYSTEMIC SCLEROSIS PATIENTS?

C. Radu, L. Groseanu, T. Gudu, A. Balanescu, D. Predeteanu, V. Bojinca, D. Opris-Belinski, A. Borangiu, I. Saulescu, S. Daia-Iliescu, C. Constantinescu, D. Mazilu, F. Berghia, M.M. Negru, V. Vlad, M. Abobului, R. Ionescu. *Internal Medicine and Rheumatology, "Sfanta Maria" Clinical Hospital Bucharest, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania*

Background: While macrovascular disease and higher cardiovascular (CV) risk are well documented in other systemic rheumatic diseases, the risk for major cardiovascular events for patients with systemic sclerosis (SSc) is yet to be established.

Objectives: The aim of the study was to determine the ability of different cardiovascular risk indices to predict major cardiovascular events (MACE) in systemic sclerosis.

Methods: The study included 144 patients followed in EUSTAR centre 096, but only patients with a follow-up for more than 10 years were selected for statistical analyses. Cardiovascular risk was estimated using QRiskII, systemic coronary risk evaluation (SCORE) and ACC/AHA risk indices. MACE were defined as: myocardial infarctions, strokes, peripheral vascular disease and cardiovascular related death. Data were compared by non-parametric tests.

Results: 32 patients, 31 females, 12 diffuse SSc subsets were included. The control group included 30 age and sex matched patients without autoimmune diseases. Mean age of the group was 52 years±SD 9.7, mean disease duration was 8 years±SD 9. The prevalence of traditional risk factors was: 13% smokers, significant family history 38%, obesity 16%, dyslipidemia 32%, older age 13%, hypertension 16%. There were no significant differences from the control group.

Major cardiovascular events were: 13% myocardial infarction, 9% peripheral vascular disease, 9% CV related deaths. Concerning CV risk indices of the 32 SSc patients, 4 (13%) were classified as having high CV risk according to QRiskII/SCORE/ACC risk.

In SSc patients, we could not identify any correlation between the above mentioned risk indices and MACE, including death of cardiovascular causes, except for a slight correlation between the SCORE and cardiovascular related death ($p=0.04$).

Conclusions: In our study, the main prediction indices were not correlated with the 10 year risk for CV events in SSc patients suggesting that we need better risk prediction tools. Both traditional risk factors and endothelial dysfunction have been proposed to participate at the onset and progression of vascular disease in SSc. Special attention should be paid to correct the traditional risk factors in combination with specific treatment for SSc.

REFERENCES:

- [1] Psarras A, Soulaïdopoulos S, Garyfallos A, Kitis G, Dimitroulas T A critical view on cardiovascular risk in systemic sclerosis. *Rheumatol Int* 2017;37(1):85–95.
- [2] Groseanu L, Bojinca V, Gudu T, Saulescu I, Predeteanu D, Balanescu A, et al. Low vitamin D status in systemic sclerosis and the impact on disease phenotype *Eur J Rheumatol* 2016;3(2):50–55.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2018-eular.7005

THU0403 SERUM LEVELS OF MACROPHAGE MIGRATION INHIBITORY FACTOR AND INTERLEUKIN-1 FAMILY CYTOKINES ARE ELEVATED IN SYSTEMIC SCLEROSIS

¹E. Lin, F. Vincent¹, J. Harris¹, R. Kandane-Rathnayake¹, G.-S. Ngian^{1,2}, J. Sahhar^{1,2}, E. Morand^{1,2}, T. Lang¹. ¹School of Clinical Sciences, Monash University; ²Rheumatology, Monash Health, Melbourne, Australia

Background: Systemic sclerosis (SSc) is an autoimmune connective tissue disorder, the pathogenesis of which remains unknown. Recent evidence suggests dysregulation of the innate immune system, particularly interleukin-(IL)–1 family cytokines. Given the emerging role of macrophage migration inhibitory factor (MIF) in pathways of IL-1 family cytokine secretion, the role of MIF, IL-1 α , IL-1 β and IL-18 in SSc is of interest.

Objectives: To examine associations between MIF and IL-1 cytokines (IL-1 α , IL-1 β , IL-18), in SSc, and associations with clinical features.

Methods: 115 SSc patients (2013 ACR/EULAR criteria) attending Monash Scleroderma Clinic and 52 healthy controls were recruited between August 2015 and August 2017. Serum MIF, IL-1 α , IL-1 β and IL-18 levels were quantified using ELISA and analysed alongside concurrent clinical and laboratory data from the Australian Scleroderma Cohort Study database

Results: Compared to controls, SSc patients had significantly elevated serum MIF and IL-18 (figure 1). A weak positive correlation was observed between MIF

and SScHAQ score ($R=0.2107$, $p=0.0437$) which was stronger in the diffuse cutaneous (dcSSc) subgroup ($R=0.457$, $p=0.0373$). Patients with elevated IL-18 levels were more likely to have active disease (EUSTAR score ≥ 3) however IL-18 was lower in patients with pulp atrophy and sclerodactyly. IL-1 β was elevated in dcSSc patients with pulmonary fibrosis and correlated with mRSS ($R=0.213$, $p=0.0254$) in all SSc patients. IL-1 α was elevated in patients with joint contractures and pulp atrophy. Positive correlations were found between concentrations of MIF and both IL-1 α and IL-1 β . However, there was no significant correlation between MIF and IL-18.

Abstract THU0403 – Figure 1. Serum cytokines in SSc patients and healthy controls. Serum cytokines (A) MIF and (B) IL-18 were measured by ELISA in healthy controls ($n=52$) and SSc patients ($n=115$). Data is presented as median $\pm$ interquartile range. Analysis was performed in Prism using the Mann-Whitney test.

Conclusions: MIF and IL-18 were significantly elevated in SSc compared to healthy controls, and IL-1 family cytokines were variably associated with clinical manifestations of SSc. A relationship between MIF and IL-1 β was confirmed. Further investigation into the roles of MIF and IL-1 family cytokines in SSc is justified.

REFERENCES:

- [1] Zhang L, Yan JW, Wang YJ, Wan YN, Wang BX, Tao JH, et al. Association of interleukin 1 family with systemic sclerosis. *Inflammation* 2014;37(4):1213–20.
- [2] van Bon L, Cossu M, Radstake TR. An update on an immune system that goes awry in systemic sclerosis. *Curr Opin Rheumatol* 2011;23(6):505–10.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2018-eular.3272

THU0404 ESOPHAGEAL INVOLVEMENT PREDICTS PULMONARY FUNCTION DETERIORATION IN PATIENTS WITH SYSTEMIC SCLEROSIS

E. De Lorenzis¹, G. Natalello¹, L. Berardini², G. Canestrari¹, L. Verardi¹, L. Gigante¹, S. Bosello¹, L. Richeldi², G. Ferraccioli¹, E. Gremese¹. ¹Rheumatology Unit, ²Respiratory Medicine Unit – Institute of Internal Medicine, Fondazione Policlinico Universitario A. Gemelli – Catholic University of the Sacred Heart, Rome, Italy

Background: Interstitial lung disease (ILD) is the leading cause of death in systemic sclerosis (SSc) but its pathogenesis and the risk factors of pulmonary function deterioration are not fully understood. Esophageal disease is high frequent in SSc and motor activity abnormalities with occult micro-aspiration of both acid and non-acid gastro oesophageal reflux has been implicated in the pathogenesis of ILD. DLCO reduction is considered the earliest sign of microaspiration-induced lung damage¹. Cross-sectional studies have demonstrated an association of SSc-ILD and esophageal abnormalities on 24 hours intraoesophageal pH-monitoring and esophageal manometry but prospective evaluation of lung deterioration is lacking^{2,3}. Esophagogram was proposed as a useful tool to evaluate disease severity of upper gastrointestinal tract involvement in SSc⁴.

Objectives: To assess the role of esophagogram in predicting pulmonary function test deterioration in SSc-patients.

Methods: We retrospectively evaluated 160 consecutive SSc patients who underwent esophagogram because of suspected upper gastro-intestinal involvement. All patients underwent baseline pulmonary function tests and global clinical evaluation. Eighty-five patients underwent a High Resolution CT within 3 months from esophagogram because of suspected lung involvement. One hundred twenty three patients underwent pulmonary function test every 6 months up to 24 months.

Results: Seventy five patients (46.9%) presented abnormalities of peristaltic waves, 50 patients (31.2%) showed structural changes (hypotonic oesophagus or dilatation) while indirect signs of cardiac incontinence (patent cardia or gastro-esophageal reflux) were present in 36 patients (22.5%). A reduced peristaltic activity with a prolongation of transit time was associated to reduced DLCO ($50.16\pm 19.80\%$ vs $60.36\pm 22.69\%$, $p=0.002$) and TLC ($87.05\pm 20.43\%$ vs $95.09\pm 20.59\%$, $p=0.017$). An hypotonic oesophagus was reported in 25.2% of patients and it was associated to ILD on CT (72.0% vs 28.0% , $p=0.033$). Patients

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.

REFERENCES:

- [1] Schachter LM, et al. Chest 2003.
- [2] Christmann RB, et al. Semin Arthritis Rheum 2010.
- [3] Marie I, et al. Arthritis Care Res 2001.
- [4] Medsger TA, et al. Clin Exp Rheumatol 2003.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2018-eular.6962

THU0405

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

F. Pignataro¹, D.P.E. Margiotta¹, G. Sambataro¹, L. Navarini¹, A. Gigante², E. Rosato², A. Afeltra¹. ¹Unit of Allergy, Clinical Immunology and Rheumatology, Campus Bio-Medico University; ²Department of Clinical Medicine, Sapienza University, Rome, Italy

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.

REFERENCES:

- [1] Pang SS, Le YY. Role of resistin in inflammation and inflammation-related diseases. Cell Mol Immunol 2006;3:29–34.
- [2] Verma S, Li SH, et al. Resistin promotes endothelial cell activation: further evidence of adipokine-endothelial interaction. Circulation 2003;108:736–40.
- [3] Gabrielli A, Avvedimento EV, Krieg T. Scleroderma. N Engl J Med 2009;360:1989–2003.
- [4] Hughes M, Herrick AL. Digital ulcers in systemic sclerosis. Rheumatology (Oxford) 2017;56:14–25.
- [5] Mihai C, Landewe R, et al. Digital ulcers predict a worse disease course in patients with systemic sclerosis. Ann Rheum Dis 2016;75:681–6.
- [6] Valentini G, Della Rossa A, et al. European multicentre study to define disease activity criteria for systemic sclerosis. II. Identification of disease activity variables and development of preliminary activity indexes. Ann Rheum Dis 2001;60:592–8.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2018-eular.4576

THU0406

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

G. Sircar¹, R.P. Goswami², D. Sircar³, D. Rath¹, S. Mondal², P.S. Mahapatra¹, A. Ghosh², P. Ghosh¹. ¹Rheumatology; ²IPGME and R, Kolkata, India; ³Nephrology, IPGME and R, Kolkata, India

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 (± 11.28) to 67.52 (± 13.59) while in Cyclophosphamide group, it declined from 59.25 (± 12.96) to 58.06 (± 11.23) at 6 months ($p = 0.003$). The change of FVC was 1.51 (± 0.45) L to 1.65 (± 0.47) L in Rituximab group compared to 1.42 (± 0.49) to 1.42 (± 0.46) L in Cyclophosphamide group. The mRSS changed from 21.77 (± 9.86) to 12.10 (± 10.14) in RTX group and 23.83 (± 9.28) to 18.33 (± 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.

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