S.10.3

PREDICTION OF CARDIAC AND VASCULAR EVENTS IN SYSTEMIC SCLEROSIS: INPUT FROM ENDOTHELIN-1 TYPE A RECEPTOR ANTIBODIES

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Objective. Cardiac and peripheral microvascular alterations are key features of systemic sclerosis (SSc). We have previously reported that angiogenic markers can predict cardiovascular outcomes in SSc (1). In parallel, a cross-sectional study reported an association between severe cardiovascular complications and functional antibodies against angiotensin II type 1 receptor (AT1R) and Endothelin-1 type A receptor (ETAR) (2). Therefore, our aim was to investigate the respective merit of all these markers in a prospective cohort.
Methods. serum levels of anti-AT1R and anti-ETAR autoantibodies, placenta growth factor (PlGF) and soluble vascular adhesion molecule (sVCAM) were measured with sandwich ELISA in a prospective cohort of 75 SSc patients. Circulating endothelial progenitor cells (EPCs) were quantified in peripheral blood by flow cytometry after cell sorting (1). The occurrence of at least one cardiac/vascular event was assessed during a planed 3-year follow-up by a composite index defined by the occurrence of at least one of the following event: a) one or more new ischemic digital ulcer (DU), b) pre-capillary pulmonary hypertension (PH) confirmed by right heart catheterization, c) left ventricular (LV) dysfunction, defined by a LV ejection fraction (EF)<50%, d) scleroderma renal crisis (SRC) (1).
Results. The mean±SD age of SSc patients (64 women) was 55±12 year old and the mean±SD disease duration was 9±8 years at baseline. Twenty-eight patients developed at least one cardiac/vascular event (DU in 18, PH in 5, LV dysfunction in 4 and SRC in a single patient). By univariate analysis, high baseline serum levels of anti-ETAR were predictive of the occurrence of cardiac/vascular events (p=0.002), together with low EPC counts (p=0.003) and increased levels of PlGF (p=0.0005) and sVCAM (p=0.009). No predictive value of anti-AT1R antibodies was identified. Multivariate analysis confirmed high serum levels of anti-ETAR antibodies (hazard ratio, HR: 3.71, 95% confidence interval, CI 1.44-9.52, p=0.03) and PlGF (HR: 5.22, 95%CI 1.96-15.87, p=0.01) as independent predictors of further development of cardiac/vascular events. The combination of high serum levels of anti-ETAR antibodies and PlGF was highly predictive of cardiac and vascular events occurrence during follow-up (HR 7.27 95%CI 2.49-23.51, p=0.0002).
Conclusion. This study identifies for the first time anti-ETAR antibodies as an independent predictor of cardiac and vascular events in SSc. This functional antibody, together with other angiogenic markers and in particular PlGF, may serve as biomarkers to improve cardiovascular risk stratification and therefore allow earlier therapeutic intervention.
References
1. Avouac *et al*., *Ann Rheum Dis* 2012.
2. Riemekasten *et al*., *Ann Rheum Dis* 2011.

Session 11: *Interstitial Lung Disease*

S.11.1

SSc-ILD: WHO TO TREAT AND HOW TO TREAT?

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Pulmonary disease is the leading cause of hospitalizations and mortality in patients with systemic sclerosis (SSc). Approximately 70-80% of patients with SSc have evidence of ILD. The majority of these patients remain relatively stable with respect to their SSc-ILD. However, in patients who have active ILD, significant loss in the lung physiology occurs early after the onset of SSc and close monitoring is warranted. This presentation will discuss the management of ILD in SSc with a focus on whom to treat, how long to treat and what pharmacological therapies to use.

S.11.2

PROGRESSIVE DETERIORATION OF PATIENTS WITH SCLERODERMA WITH PULMONARY INVOLVEMENT: 11-YEAR OUTCOMES FROM THE SCLERODERMA LUNG STUDY (SLS1)

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Background. SLS1 was a 13 site pivotal clinical trial showing benefit in lung function, skin thickening and quality of life measures after a 1-year course of oral cyclophosphamide (CY) (Tashkin, *et al*. NEJM 2006). From 2000 to 2004, 158 subjects with diffuse or limited scleroderma, active alveolitis and an FVC of

Table I. Long-term Outcomes in the Scleroderma Lung Study.

		Time (Months) to 50% Survival (95%) CI)	
Factor at Randomization	Number of Subjects	Death	Survival Free of Organ Failure
Treatment			
Cyclophosphamide	79	115 (92, NA)	98 (79,132)
Placebo	79	NA* (105, NA)	90 (62,122)
Patient Age (yrs)			
<40	42	138 (86, NA)	92 (81, NA)
>=40	115	126 (100, NA)	97 (72, 122)
Disease Extent			
Diffuse	94	119 (89, NA)	90 (70, 115)
Limited	64	138 (106, NA)	126 (79, 132)
Disease Duration (yrs)			
<3	85	126 (79, NA)	89 (58, 132)
>=3	71	128 (97, NA)	105 (81, 128)
Smoking History			
No	86	133 (115, NA)	97 (81, 128
Yes	58	138 (70, NA)	98 (57, 132)
Rodnan Skin Score			
<16	94	138 (126, NA)	126 (85, 133)
>=16	64	97 (64, NA)	77 (51, 100.0
DLCO (% predicted)			
<45	75	97 (77. 138)	79 (52, 90)
>=45	83	NA* (119, NA)	132 (111, NA)
FVC (% predicted)			
<65	53	83 (52, NA)	
>=65	105	133 (115, NA)	

NA* Indicates that the survival probability is >50% at all available time-points.

45-85% predicted were randomized to CY or placebo. At year two (one year off study drug), benefits dissipated and follow-up was discontinued.
Objectives. To determine late outcomes in this well defined scleroderma population.
Methods. Protocol and telephone interview scripts were IRB approved at SLS sites. Staff searched two public death registries for all subjects. Data included dates of organ failure (oxygen use, cardiac ablation or pacing, lung, cardiac, kidney or stem cell transplant, dialysis or TPN), cancer development, and employment and Eastern Oncology Group (ECOG) performance status. Kaplan Meier (KM) estimates were censored at death or date last known alive.
Results. Of 158 study participants, 40 survive without organ failure, 18 survive with organ failure, 66 are deceased, 2 have no available data and 32 (20%) were unreachable, not in death registries, and dates recorded for last known alive. Organ failure developed in 33 subjects (14 CY and 19 placebo) with 31 experiencing lung failure. Seven CY and six placebo recipients developed cancer. Physical performance was significantly impaired in 28 (48%) of the 58 survivors: 5 were fully active; 26 were ambulatory but restricted in strenuous activity; 21 were ambulatory and capable of self care but unable to carry out work activities; and 7 were capable of only limited self care. Twenty-eight (48%) of survivors reported they were unemployed due to health reasons. Twenty-two (14%) of the 158 subjects are known to be alive and free of organ failure or significant physical impairment. In Table I, times to 50% survival are presented by baseline characteristics. Decreased DLCO, decreased FVC and increased Rodnan scores at randomization were associated with significantly shorter durations of organ failure-free survival. Figure 1 depicts the 11-year KM probability of organ failure-free survival by treatment.
Conclusions. The SLS1 cohort showed progressive mortality, organ failure and physical impairment in both treatment arms. At the time of data collection, only 14% were known to be alive and free of significant physical impairment or organ failure. A 1-year course of CY did not provide long-term benefit and better treatments are needed for scleroderma lung disease.

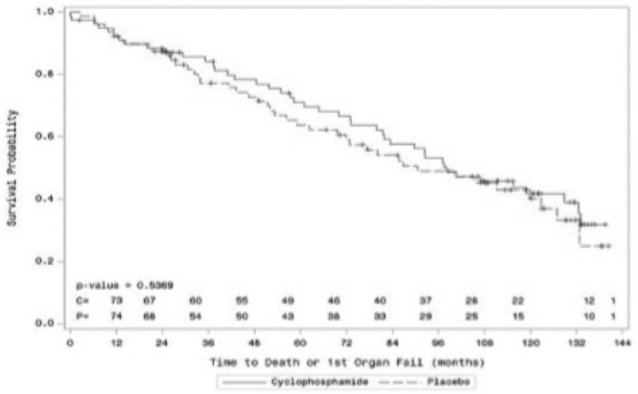

Fig. 1.

S.11.3

SURVIVAL AFTER LUNG TRANSPLANTATION IN SYSTEMIC SCLEROSIS. A SYSTEMATIC REVIEW

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Background/Purpose. Lung transplantation is a life-saving option for systemic sclerosis (SSc)-associated pulmonary arterial hypertension (PAH) and interstitial lung disease (SSc-ILD) patients. Yet, there is risk of post-transplantation mortality. The objective of this study was to evaluate survival of SSc patients post-lung transplantation. We secondarily evaluated SSc lung transplant recipient characteristics, and compared post-lung transplantation survival of SSc patients to non-SSc patients (idiopathic PAH, and ILD).
Methods. A systematic review of MEDLINE, EMBASE, Cochrane Central Registry of Controlled Trials and CINAHL (all inception to 2012) was performed to identify studies evaluating post-lung transplant survival in SSc compared to non-SSc patients. Two reviewers independently abstracted study and survival data using a standardized form.
Results. 226 citations were screened to identify 7 observational studies reporting SSc patients who underwent single lung, double lung, or heart-lung transplantation. Mean age at transplantations ranged 46-53 years. SSc post-transplantation survival ranged 69%-91% at 30-days, 69%-85% at 6-months, 59%-93% at 1-year, 49%-80% at 2-years, and 46%-79% at 3-years. ILD post-transplant survival was 80% at 30-days, 80%-90% at 6-months, 59%-83% at 2-years, and 69% at 3-years. IPAH post transplant survival was 79% at 30-days, 79%-90% at 6-months, and 74%-90% at 1-year. The reporting of overlapping cohorts potentially including the same patients precluded meta-analysis. Causes of death in SSc patients, when reported, included graft failure (n=6), infection (n=8), cardiac events (n=3), hemorrhagic stroke (n=1), respiratory failure (n=3), malignancy (n=2), pulmonary hypertension (n=1), complications of bronchiolitis obliterans syndrome (BOS) (n=1), anesthetic complication (n=1), and scleroderma renal crisis (n=1). There were no reports of recurrence of SSc in the lung allograft.
Conclusion. SSc survival post-lung transplantation is very good, and improving with time. The short-term and intermediate-term survival post-lung transplantation are similar to IPAH and ILD patients requiring lung transplantation. Future researchers should delineate the access process for lung transplantation and report the occurrence of acute rejection, infection, bronchiolitis obliterans syndrome, renal dysfunction and dialysis, gastroparesis, and need for tube feeding.

S.11.4

GENETIC MARKERS OF SUSCEPTIBILITY AND INTERSTITIAL LUNG DISEASE IN SYSTEMIC SCLEROSIS PATIENTS: AN IMMUNOCHIP STUDY

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Objectives. We analyzed 186 known autoimmune risk loci finemapped in the Immunochip custom array with the aim to identify novel SSc risk loci shared with other autoimmune diseases and to narrow down previously SSc associated loci. Moreover, we intended to establish firm genetic markers for interstitial lung disease in SSc patients.
Methods. We genotyped 1,959 SSc cases and 3,582 controls of European ancestry from the United States and Spain using the Immunochip custom array. Classical HLA alleles, amino acid residues and SNPs imputation were performed and a fitting model for the association in the HLA region was defined using conditional logistic regression analyses. In addition, eight SNPs were chosen for replication in 4,017 SSc cases and 5,935 controls from 6 additional populations of European ancestry, reaching a combined population of 5,876 SSc cases and 9,517 controls. Furthermore, a pulmonary involvement case-case analysis was performed con-

sidering the interstitial lung disease (ILD) status of the SSc patients (determined using HRCT). For this phenotype-specific analysis, Immunochip genotype data were available for 589 ILD+ SSc patients and 1,333 ILD- SSc patients from 4 European cohorts.
Pooled analysis of the discovery populations with the replication cohorts was performed using the inverse variance method under a fixed effects model. Significance threshold was established at the genome-wide level (p<5x10-8).
Results. We identified a model comprising 6 polymorphic amino acidic positions and 7 SNPs that explained the observed significant associations in the HLA region. Moreover, we identified 3 novel SSc risk loci showing genome-wide level associations. These novel loci included: DNASE1L3, SCHIP1 | IL12A and ATG5. Remarkably, the association of the rs35677470 functional missense variant in the DNASE1L3 locus with the ACA+ subset of patients is the most significant non-HLA association with SSc revealed to date (p=2.70x10-32 OR=2.00). In addition, we further refined the area of association for the STAT4, IRF5/TNPO3 loci and related an observed peak of association in the PXK gene to the novel DNASE1L3 locus. Seven SNPs showed suggestive p-values in the ILD+ versus ILD- patient analysis and a replication step comprising 497 ILD+ and 853 ILD- patients is in progress.
Conclusions. This study provided a comprehensive insight into the association of the HLA region with SSc, identified 3 new SSc susceptibility loci and proposed new candidates for SSc-related ILD.

Session 12: *Pulmonary Arterial Hypertension*

S.12.1

PAH: HOW TO MAKE THE RIGHT DIAGNOSIS AT THE RIGHT TIME

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With the availability of effective targeted therapies for pulmonary arterial hypertension associated with systemic sclerosis (SSc-PAH), the detection of early stages of SSc-PAH has become a major task for the treating physicians. The most frequent diagnostic measures used in clinical practice to detect suspected PAH are lung function tests with DLCO and transthoracic echocardiography. However, while in advanced stages echocardiography might be a useful tool to suspect PAH, accumulating data show that standard echocardiography as a single measure is insufficient to detect PAH in early or even preclinical stages. These findings have let to different initiatives trying to establish recommendations and screening algorithms for the early detection of SSc-PAH. Recommendations were based on different consensus methods such as Delphi exercises and the RAND/University of California, Los Angeles consensus methodology. Evidence-based data were derived from multicenter studies with multivariate regression analysis and resulted in prediction scores such as the DETECT-score for PAH and the Cochin Risk prediction score for PH. These and other recommendations and prediction scores will be presented and their use in clinical practice will be discussed in this presentation. Most importantly, right heart catheterization remains the gold standard for the diagnosis of PAH

S.12.2

CHARACTERISTICS OF SYSTEMIC SCLEROSIS PATIENTS WITH PULMONARY HYPERTENSION AND A PULMONARY CAPILLARY WEDGE PRESSURE >15 IN THE PHAROS REGISTRY

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Background. Systemic sclerosis (SSc) commonly leads to pulmonary hypertension (PH), which may be associated with left heart disease and an elevated pulmonary capillary wedge pressure (PCWP). Patients in this PH subgroup may have mean pulmonary artery pressures (mPAP) in proportion to their elevated PCWP (pulmonary venous hypertension, "PVH") or higher than expected given their PCWP ("out-of-proportion PH"). It is not known what causes this difference in patients with SSc.
Methods. Baseline characteristics from 48 patients in the PHAROS registry who had a PCWP>15 on right heart catheterization (RHC) were retrospectively analyzed. Characteristics of those who died before 2 years of follow-up (n=10) were compared to those who were alive at 2 years (n=20). Patients were divided into 2 groups based on their initial RHC diastolic pressure gradient (DPG=diastolic PAP minus PCWP): PVH (DPG<5mmHg) or out-of-proportion PH (DPG>5mmHg). Comparisons were made between groups using unpaired t-tests or Chi square. Kaplan-Meier analysis compared survival and time to first hospitalization.
Results. At baseline, the mPAP was 36.8±11.8 mmHg and the PCWP was 19.4±3.3mmHg. Univariate factors associated with death prior to 2 years are shown in the table. In multivariate analysis, the only independent factors associated with death prior to 2 years were lower 6MWD (p=0.01) and higher PCWP (p=0.01). The out-of-proportion PH group (n=26) had higher baseline mPAP (42.7±13.0 vs. 29.7±3.7mmHg, p<0.0001), DPG (12.7±8.6 vs. 2.9±1.5mmHg, p<0.0001), and pulmonary vascular resistance (376±235 vs. 204±101 dynes/sec/cm5, p=0.003) compared to the PVH group (n=22). Although there was no difference in baseline immunosuppression use overall, mycophenolate (MMF) use was less common in the out-of-proportion PH group (8% vs. 37%, OR 0.15, p=0.027). There were no differences between the PVH and the out-of-proportion PH groups in age, sex, disease duration, pulmonary function, SSc subtype, or 6MWD (all p>0.05). There was no difference in 3-year survival between the 2 subgroups (PVH: 1-year=95%, 3-year=61%; out-of-proportion PH: 1-year=85%, 3-year=63%, p=0.73). There was a trend towards shorter time to first hospitalization in the out-of-proportion PH group (p=0.13).
Conclusion. In patients with SSc-PH and a PCWP>15, lower 6MWD and higher PCWP were independently associated with an increased risk for death within 2