the stable cGMP analogue 8-Bromo-cGMP and stimulated with TGFβ. Crosstalk between sGC signaling and TGFβ signaling was studied by levels of phosphorylated SMAD2 and 3 (IF, WB), SMAD-reporter activity and target gene expression. In vivo, we investigated the anti-fibrotic activity and the tolerability of sGC stimulation in bleomycin-induced skin fibrosis, tight skin-1 mice, and mice challenged with an adenovirus expressing a constitutively active TGFβ receptor I (TBR model).
Summary of the results. When assessing the anti-fibrotic activity of the sGC, we observed that sGC stimulation by BAY41-2272 inhibited TGFβ-dependent fibroblast activation and collagen release from SSc and healthy fibroblasts in a dose dependent manner. In addition, sGC stimulation was effective in preventing the development of skin fibrosis and reversing established skin fibrosis in the bleomycin model and in tight skin-1 mice. sGC stimulation was well-tolerated and did not have significant effects on systemic blood pressure and heart rate as indicated by telemetry studies. Mechanistically, sGC knockout fibroblasts confirmed that the sGC is essential for the anti-fibrotic effects of BAY41-2272. Furthermore, we observed that 8-Bromo-cGMP mimicked the effects of BAY41-2272 and reduced TGFβ-dependent collagen release. Nuclear p-SMAD2 and 3 levels, SMAD-reporter activity, and transcription of classical TGFβ target genes remained unchanged upon sGC stimulation, suggesting that the anti-fibrotic sGC activity is independent of canonical TGFβ-signaling. In TGFβ-driven experimental fibrosis (TBR model), sGC stimulation inhibited TGFβ-driven fibroblast activation and collagen release, but did not change p-SMAD2 and 3 levels and TGFβ target gene expression, confirming that non-canonical TGFβ cascades mediate the anti-fibrotic sGC activity.
Conclusions. We identified a novel anti-fibrotic role of the sGC. sGC activity increases cGMP levels, blocks non-canonical TGFβ signaling and inhibits fibrosis in various model systems of SSc. Since sGC stimulators have shown excellent efficacy and tolerability in phase 3 clinical trials for PAH and CTPH, they may be further developed for the simultaneous treatment of fibrosis and vascular disease in SSc.

Session 10: *Cardiovascular Involvement*

S.10.1

CONDUCTION AND RHYTHM DEFECTS IN SCLERODERMA

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Signs or symptoms of arrhythmias or conduction defects are frequently reported in patients with systemic sclerosis. These rhythm disorders may have several origins (i.e. related to primary heart involvement, pericardial disease, valvular regurgitation, pulmonary arterial hypertension…) and may negatively affect the overall prognosis of these patients. It is important to identify patients at high risk for cardiac arrhythmias thanks to a complete cardiologic evaluation, find out the underlying heart disease including SSc related myocardial involvement; in addition, some therapeutics options in SSc patients may differ from that are recommended on other population

S.10.2

IMPROVEMENT OF DIGITAL ULCERATIVE DISEASE IN PATIENTS WITH SYSTEMIC SCLEROSIS IS ASSOCIATED WITH BETTER FUNCTIONAL PROGNOSIS

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Background/Objective. Ischemic digital ulcers (DU) represent a major complication of systemic sclerosis (SSc) leading to hand disability. We investigated the impact of controlling the ulcerative disease on hand disability and quality of life after one year in SSc patients treated with bosentan.
Methods. ECLIPSE is a 2-year prospective, observational study. Patients with SSc who experienced at least one DU in previous year and received bosentan were included between October 2009 and March 2011. Demographical and clinical data were collected at inclusion and at 1 year, as well as disability scores (Cochin hand function scale (CHFS), health assessment questionnaire disability index (HAQ-DI)), pain score (Visual Analog Scale), and quality of life (SF-36). A controlled ulcerative disease was defined by the absence of new ulcer between inclusion and one-year follow-up. Data are presented as means ± standard deviations.
Results. Follow-up data were available at one year for 120 patients out of the 190 included patients. Patients' characteristics were similar to those of the overall cohort. Mean ages at inclusion and SSc diagnosis were 54±15 and 44±15 years, respectively. SSc was diffuse in 42% of the cases. At inclusion, patients had been receiving bosentan for 15.6±22.1 months. During the one-year follow-up, 46 (38%) patients experienced a new DU and the incidence of the event was 0.6 event/patient-year [95% confidence interval: 0.44-0.81]. Nevertheless, the proportion of patients with DU decreased from 61% to 22% and the number of DU per patient decreased from 1.4±1.8 to 0.6±1.6 (p<0.0001). This diminution was associated with a significant decrease in disability scores from 29.4±20.1 to 25.0±20.2 (p=0.005) on the CHFS and from 0.96±0.68 to 0.88±0.73 (p=0.04) for the HAQ-DI; the pain score decreased from 4.3±3.1 to 2.9±2.8 (p<0.0001). Improvements in the physical and mental components of the SF-36 were non-significant except for bodily pain (p=0.04) and mental health (p=0.01).
Patients with a controlled ulcerative disease (n=58) significantly improved CHFS (p=0.04), HAQ-DI (p=0.04), and physical component of the SF-36 (p=0.05) compared with patients with an uncontrolled disease (n=62).
During the one-year follow-up, 21 (17%) patients discontinued bosentan for an adverse event including 5 patients presenting elevated aminotransferases.
Conclusion. In patients with SSc receiving bosentan, a controlled ulcerative disease is associated with a significant attenuation of disability.

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.