# EULAR 2018 Systemic Sclerosis Highlights – Clinical Practice

## A EUSTAR Young Investigator Group Report

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Exciting clinical research was presented at the meeting, especially advances in the fields of imaging, risk prediction models and more personalised approaches to intervention for patients with SSc.

Clinical practice

A review of the medical records of US patients with SSc from 1980 to 2016 found no change in incidence over the 36-year period of study. Mortality remains worse than for the general population with no evidence of improved survival over time [1]. Regarding disease subset, there was an analysis investigating skin and lung involvement trajectories of limited cutaneous SSc (lcSSc) using the large European Scleroderma Trial and Research (EUSTAR) database [2]. Worsening skin fibrosis was observed in a limited number of 6.4%, 7.8% and, respectively, 9.8% at 6, 12 and 24 months follow-up, whereas worsening of ILD was observed in a substantial number of patients, 11.7% and 19.9% with ILD at baseline, at 12 and 24 months follow-up respectively. In multivariate analysis, variables predicting ILD progression at 24 months were EScSG-AI >3 (OR [95 IC]: 3.8 [1.51–9.56], p=0.005), FVC (1.03 [1.01–1.04], p<0.001) and LVEF (0.91 [0.85–0.97], p=0.005), supporting the inclusion of lcSSc patients in SSc-ILD trials evaluating anti-fibrotic drugs [2]. Muscle function and endurance in several joints and shoulder-arm active range of motion were reduced in comparison with reference values. Patients with moderate to end-stage lung disease were more impaired compared to no or mild lung disease in an analysis of 205 patients with SSc [3]. Another study assessed health professional (HP) treatment from the perspective of SSc patients regarding the referral process, use of care provided by HP, treatment targets and outcome satisfaction [4], concluding that although a significant number of patients (156(73%)) reported high satisfaction with occupational therapy, saying they could cope better with their complaints after the treatment and reported improvement in their daily activities, there was suboptimal referral and communication between rheumatologists and HP [4]. An online survey to evaluate worldwide agreement of the updated recommendations for treatment of SSc among SSc experts concluded that, in general, worldwide agreement is high; differences in agreement are partially explained by geographical area and local drug availability [5].

Risk prediction models

Recent work to establish the best threshold of the modified Rodnan skin score (mRSS) to identify patients with progressive skin disease led to an analysis on the ethnically diverse cohort Texas-based GENISOS cohort, which also includes a large proportion of Pol3-positive patients, reconfirmed that setting a lower upper threshold of mRSS at study inclusion increases the proportion of skin disease progressors and reduces the absolute number of regressors [6]. The authors proposed a mRSS cut-off of ≤27, which had the highest probability of progression (odds ratio 9.1, 95% confidence interval 1.2–70.9, p<0.035, area under the curve 0.652). Progressors were more frequently positive for anti-topoisomerase antibodies (37.5% vs. 15.3%, p=0.028), negative for anti-Pol3 antibodies (93.8% vs. 62.3%, p<0.012), had a shorter disease duration (median, Q1-Q3: 1.3, 0.5–2.2 vs. 2.4, 1.1–3.5 years, p<0.005) and lower mRSS (median, Q1-Q3: 21, 11–25 vs. 24, 16–31, p<0.012) than non-progressors [6].
Another study from the EUSTAR cohort tried to identify factors associated with mortality and worsening of organ function in diffuse cutaneous SSc (dcSSc) patients, to allow enrichment in clinical trials [7]. The final prediction model included age, active digital ulcers, C-reactive protein elevation, significant dyspnea, lung fibrosis, muscle weakness, pericardial effusion and proteinuria. [7].
One study on 99 SSc patients evaluated if macrovascular damage (manifest as ulnar artery occlusion (UAO)) is associated with microvascular damage and with the occurrence of new digital ulcers (DU), cardiovascular events and mortality [8]. UAO was associated with markers of microvascular damage, such as late nailfold capillaroscopy pattern (33.3% vs 6.8%; OR=6.88, 95% CI=1.76 to 26.82; p=0.03) and was predictive of new ischaemic DU (44.5% vs 24.8%; HR=2.23, 95%CI=1.02 to 4.86; p=0.037), however, it was not associated with traditional CV risk factors and did not predict CV events, pleading for a SSc specific vasculopathy [8].
A study examining clinical and echocardiographic parameters (including left ventricular global longitudinal strain (GLS)) associated with all-cause mortality and cardiovascular (CV) events in SSc patients [9]. In multivariate Cox-regression analyses, age, female sex , NT-proBNP, DLCO and GLS were independently associated with mortality. After dividing patients into groups according to median GLS (−20.9%) and elevated NT-proBNP

(>200 ng/L), survival rates were lower and cardiovascular events increased when GLS was impaired and worsened when NT-proBNP was elevated (Log-rank p<0.001) [9]. A separate study evaluated in SSc patients (free of CV risk factors and CV disease (CVD)) the prevalence, clinical association and natural history of cardiac MRI (CMR) abnormalities over 3 years, and found that extracellular volume (ECV) increased in patients with ILD [mean diff.(CI) 3 (-1,6),p=0.14] and in those with higher mRSS at baseline (r=0.455,p=0.04), whereas a significant decrease over the 3 years was observed in LV end-diastolic volume (LVEDV/BSA), LV end-systolic volume (LVESV/BSA) and left ventricular stroke volume (LVSV/BSA). A decrease in LVEDV/BSA was noticed for those with a history of DU [mean diff.(CI) −5(−12,2), p=0.1], ILD [mean diff.(CI) −6(−12,0.5),p=0.07)] and shorter disease duration (r=-0.504, p=0.02) [10]. An international, multicentre, longitudinal study on 180 SSc patients tried to identify a combined index predictive of significant weight loss at 12 months employing Malnutrition Universal Screening Tool (MUST) and serum adiponectin to leptin ratio (A/L) [11]. Logistic regression analysis identified the combination of BMI and A/L as the best PREdictor of MAlnutrition in Systemic Sclerosis (PREMASS). The formula 12.18-(0.63*BMI)+(1.51*A/L) predicted the end point with AUC=0.91 (95% CI:0.77–0.84). A PREMASS score >0.23 showed 91.3% sensitivity (95% CI:79.79–100) and 80.46% specificity (95% CI:72.13–88.79) for >10% weight loss with an overall 55.26% positive predictive value (PPV) (95% CI:39.45–71.07) and 97.22% negative predictive value (NPV) (95% CI:93.43–100) and a relative risk (RR) of 19.90 (95% CI:4.93–80.37) [11].

Imaging

Pulmonary ultrasound (US) was performed in 133 SSc patients to detect subclinical ILD [12]. At baseline, 54 SSc patients showed US signs of subclinical ILD, and 30 of them presented worsening at 6-9 months follow-up. Moreover, US correlated with HRCT ILD, but not with chest X-ray [12]. Another US study evaluated the prevalence of entheseal and Synovio-Entheseal Complex (SEC) modifications in 30 SSc patients and 12 controls [13]. The entheseal sites were the lateral epicondylar common extensor tendons (CET), and sites of the Glasgow Ultrasound Enthesis Scoring System (GUESS. In SSc, GUESS scores were significantly higher than in controls and the CET entheses of SSc patients showed significantly more US B-mode alterations than controls. CET enthesitis was correlated with SEC inflammation, but not with disease characteristics [13].

A study assessing gastrointestinal involvement with a combination of positron emission tomography and magnetic resonance imaging, suggested these could be used for detecting GI fibrosis, especially in early stages [14]. Mean T1 values on MRI for the large and small bowels were significantly higher in SSc patients than in healthy controls (large bowel: 1113±189 ms vs 856±182 ms respectively, p=0.0006; small bowel: 1331±246 ms vs 1169±123 ms respectively, p=0.0296), indicating the presence of GI fibrosis. Mean PET SUV values for the large bowels were also higher in SSc patients than in healthy controls (1.12±0.23 vs 0.82±0.23 respectively, p=0.0217) [14]. Another study compared esophageal dilatation observed with CT to manometry in SSc and healthy controls [15]. Esophageal proximal diameter in the coronal plane was good for detecting esophageal dysmotility (0.798, 95% CI 0.705–0.890), suggesting CT done in the daily clinical practice could be exploited when manometry is not possible [15].

Autoantibodies

There was an analysis that found the continuous presence of IgM anti-topoisomerase 1 antibodies (ATA-IgM) to be associated with disease progression (59% of patients with positive ATA-IgM vs. 15% with negative ATA-IgM, p=0.02), defined as increase of modified Rodnan Skin Score (mRSS) with ≥5 points, progression of pulmonary involvement (-≤10% of predicted forced vital capacity [FVC] or diffusion capacity of the lung [DLCO]), development of digital ulcers, renal crisis, pulmonary arterial hypertension and/or mortality [16].

The selection of abstracts reported here provides a synopsis of some of the exciting and influential research presented at the 2018 EULAR Congress. Inevitably, an exercise such as this is inherently subjective and will inadvertently omit important research. Nonetheless, we hope to have compiled a selection of the meeting's highlights whose manuscripts we eagerly await.

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