ACR 2017 Systemic Sclerosis Highlights – Clinical Practice

A EUSTAR Young Investigator Group Report

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A large amount of new clinical research was presented at the meeting that has the potential to deliver novel biomarkers, improved risk prediction models and more personalised approaches to intervention for patients with SSc over the coming years.

Clinical practice

A retrospectively analsysis of transplant registry data has suggested lung transplantation is being increasingly considered in the management of SSc since data on favourable outcomes following transplantation emerged [1]. A preliminary analysis of the the US prospective early diffuse SSc PRESS cohort has suggested cardiopulmonary complications are the main causes of death in early dcSSc [2]. An assessment of autonomic dysfunction suggested a possible association between orthostatic intolerance and secretomotor dysfunction with severe gastrointestinal involvement in SSc [3]. A study of body image dissatisfaction identified younger age, diffuse SSc and the presence of hypo/hyper-pigmentation as being associated with high levels of body image dissatisfaction [4]. Patients who reported being distressed by their appearance also had greater scores on measures of disability, depressive and anxious symptoms [4]. Clinical data from the aforementioned GRASP cohort confirmed earlier assumptions that SSc is associated with more severe disease in black people. There is a higher prevalence of diffuse cutaneous disease and scleroderma renal crises in African Americans compared with predominantly Caucasian European patients enrolled in the EUSTAR cohort [5]. Furthermore, African American patients with SSc have a higher prevalence of severe fibrosis on HRCT, lower FVC % and DLCO %, pulmonary hypertension, severe cardiac involvement, SRC, and higher mortality during follow-up (21.1% vs 11.1, p=0.006) [6].

Risk prediction models

Further attempts at developing a risk prediction model for predicting PAH development in 12 months in a large SSc cohort [7]. Multivariate prediction models included age, presence of ILD and specific SSc antibodies (anti-U3RNP and anti-RNA polymerase). Older age, anti-RNA polymerase and anti-U3RNP antibodies and lower DLco predicted a higher risk for PAH [7]. Another study elucidated factors associated to worse prognosis in both idiopathic and SSc-related PAH [8]. Overall survival was lower in SSc-related PAH compared with idiopathic PAH (5.33 vs. 10.26 years median survival). In SSc-PAH patients, age <63years, systolic blood pressure on the right heart catheterization <125 mmHg and cardiac index (CI) determined by thermodilution lower than 2.5 L/min/m2 were factors associated with worse survival [8]. A separate study examined echocardiographic parameters that were predictive of PAH progression and all-cause mortality [9]. Higher age, lower DLco, presence of pericardial effusion, higher left atrium area and lower tricuspid annular plane systolic excursion were each associated with mortality [9]. PAH progression was related to age, lower DLCO and right atrium area [9]. This theme was further explored in a longitudinal assessment from the DETECT study cohort [10]. During a median of 12.6 months follow-up, 43.9% had a combined endpoint disease progression. Male gender (OR 4.1), high Forced Vital Capacity (FVC) % predicted/diffusing capacity for carbon monoxide (DLCO) % predicted ratio (OR 3.6), high Borg dyspnoea index (1.7) were each associated to PAH progression, as well as a low DLCO % predicted [10]. Other work examined factors predicting future progression of SSc-ILD [11]. Logistic regression identified a poor SpO2 during 6-minute walk test (OR 0.78) and arthritis (OR 7.15) as potential predictors of ILD progression at 1 year [11].

Two large registry analyses examined predictors of disease progression. The first focussed on progression of internal involvement over 12 months in patients with early diffuse SSc [12]. A higher skin score was associated with worse Medsger's disease severity score without skin evaluation, physician and patient global numerical rating scales, and S-HAQ, functional disability in HAQ-DI and poorer quality of life measured with SF-36 PCS [12]. It also correlated with presence and severity of tendon involvement, gastrointestinal disease and S-HAQ digiltal ulcer severity and intestinal problems items [12]. A higher baseline mRSS also predicted worse function HAQ-DI, quality of life in SF-36 PCS, Medsger's severity score and severity of joint involvement at 1-year follow-up [12]. An analysis of disease progression in patients enrolled in the European Scleroderma Trial and Research (EUSTAR) group database, meanwhile, identified higher age, active digital ulcers, C-reactive protein elevation, significant

dyspnoea, lung fibrosis, muscle weakness, pericardial effusion and proteinuria as being predictive of disease progression at 1-year [13].

Biomarkers

CCL21 was evaluated as a novel biomarker for predicting the presence of PAH and future outcomes in a large cohort of 326 SSc patients [14]. Multivariate analysis confirmed associations between CCL21 levels and existing PAH (HR 5.1, p<0.001), new PAH onset (HR 3.3, p=0.003) and the future occurrence of PAH related events (HR 4.7, p<0.001) [14]. Poor 5- and 10-years survival was observed in patients with high CCL21 levels (87% and 71% vs 96% and 91%, p<0.001) [14]. Another study examined the potential role of biomarkers of collagen degradation (C3M, C4M2) and collagen formation (PRO-C3) for the diagnosis and prediction of progression of both ILD and skin thickening [15]. Logistic regression analysis identified pro-C3/C3M ratio as predictor of lung deterioration (OR 3.8) and skin progression (OR 2.1) [15]. The findings suggest collagen turnover biomarkers may emerge as useful diagnostic and prognostic tools in SSc.

Imaging

The ultrasonographic renal resistive index (RRI) was performed in 255 SSc patients to evaluate its correlation with organ involvement and to predict clinical worsening [16]. A RRI <0.7 was related with renal function, systolic pulmonary arterial pressure, E/A ratio, DLco and late capillaroscopy pattern [16].

Autoantibodies

There were large analyses of the clinical phenotype of SSc patients with or without anti-Th/To autoantibodies confirming its association with Caucasian patients, minimal skin involvement and pulmonary arterial hypertension (PAH affecting 21%) [17]. Despite the association with PAH there were not differences in 5-year cumulative survival (29% vs 28%) [17].

The selection of abstracts reported here provides a synopsis of some of the exciting and influential research presented for the first time at the 2017 ACR Annual Meeting.

Inevitably, an exercise such as this is inherently subjective and will inadvertently omit important research findings whose significance will have important and far-reaching effects on our understanding of scleroderma and related disorders in the future. Nonetheless, we hope we have compiled a selection of some of the meeting's highlights whose full manuscripts we shall eagerly await. We hope this synopsis will be of interest to investigators who could not attend the meeting in person and alert interested clinicians and investigators to eagerly awaited manuscripts that shall provide a more detailed account of the important work.

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