Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2021-eular.330

S100A4 PLASMA LEVELS CORRELATE WITH DISEASE ACTIVITY, SKIN FIBROSIS AND INTERSTITIAL LUNG DISEASE IN SYSTEMIC SCLEROSIS PATIENTS

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Background: In our previous study we demonstrated that S100A4 is overexpressed in scleroderma (SSc) skin, SSc fibrilloblasts and preclinical models of SSc in a TGF-β dependent manner. We showed that S100A4 is a new regulator of TGF-β signalling and its inhibition prevents the pro-fibrotic effects of TGF-β. Inactivation of S100A4 prevented dermal fibrosis induced by bleomycin and in Tsk-1 mice.

Methods: A total of 33 patients (29 females; mean age 52.8 years; disease duration 4.2 years; dcSSc/lcSSc = 8/25) who met the 2013 EULAR/ACR classification criteria for SSc and 20 healthy age- and sex-matched individuals were included in this study. Plasma levels and S100A4 expression were analysed using ELISA (CUSABIO, Houston, USA). Data are presented as median (IQR).

Results: S100A4 plasma levels were significantly increased in SSc patients compared to healthy controls (78.6(32.3-146.5) vs. 43.4(32.3-53.4) ng/mL; p=0.011). Patients with diffuse cutaneous (dc)SSc had significantly higher levels of S100A4 than patients with limited cutaneous (lc)SSc or healthy controls (168.5(81.5-347.5) vs. 63(30.9-130.6) p=0.017; p=0.001, respectively). Plasma levels of S100A4 positively correlated with mRSS (r=0.556, p=0.001). Furthermore, S100A4 positively correlated with ESSG activity score (r=0.750, p=0.001). However, only correlations between S100A4 and mRSS, and ESSG activity score were approved at corrected level of statistical significance after Bonferroni’s correction (p<0.01). In a prospective analysis of patients (n=40) with progressive SSc-ILD treated with 6 (n=24) or 12 (n=16) monthly i.v. pulses of cyclophosphamide (CPA, 500 mg/m2), we observed a significant decrease in plasma S100A4 levels between the baseline samples (month 0) and blood drawn after 6 months of CPA treatment (76.3(52.9-98.6) vs. 73.2(44.9-98.6) ng/mL, p=0.013). Furthermore, baseline S100A4 levels predicted the change (m0-m6) in CRP and ESR levels after 6 months of CPA therapy (r=0.472, p=0.004; r=0.528, p=0.003, respectively).

Conclusion: We demonstrate that plasma S100A4 levels are significantly increased in SSc patients compared with healthy controls. Increased S100A4 is associated with the dcSSc subset, skin involvement, deteriorated parameters of interstitial lung diseases and higher disease activity in patients with progressive SSc-ILD. S100A4 declines after 6 months of cyclophosphamide therapy and predicts the systemic inflammatory response. These data further support our previous findings on the role of S100A4 as a regulator of TGF-β induced fibrosis in SSc.

S100A4 levels correlated with disease activity, skin fibrosis and interstitial lung disease in systemic sclerosis patients

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Background: As a rare, complex, and heterogeneous disease, mixed connective tissue disease (MCTD) represents a challenge for clinical practice.

Methods: We analysed the prospectively collected MCTD cohort at our tertiary referral centre. The patients’ medical histories were investigated for fulfilment of Sharp’s criteria (1990) and/or ACR/ESRAS criteria (2005) of MCTD.

Results: Out of 85 patients initially referred as MCTD, only one third fulfilled the diagnostic MCTD criteria. Most of the remaining patients had different CTD (29%) or overlap syndromes (20%). In our final cohort of 33 MCTD patients, 6 (48%) also met the classification criteria of systemic sclerosis, 13 (39%) those of systemic lupus erythematosus (SLE), 6 (18%) those of rheumatoid arthritis, and 3 (9%) those of primary myositis. Over the median observation period of 4.6 (1.6, 9.9) years, only two patients (6%) underwent disease conversion from MCTD to SLE and no patient converted towards other diseases. The number of patients in remission increased from 6 (18%) to 15 (45%) due to introduction of immunosuppressive treatment. Combination therapy was favoured in most cases (17 patients, 52%), whereas monotherapy was less frequent (12 patients, 36%), and only 4 (12%) patients remained without immunosuppressive treatment for the entire follow-up period. Hydroxychloroquine, prednisone, and methotrexate were the most frequently used medications in our cohort.