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SERUM INTERFERON SCORE PREDICTS CLINICAL OUTCOME AT 12 MONTHS IN DIFFUSE CUTANEOUS SYSTEMIC SCLEROSIS AS MEASURED BY GLOBAL RANKED COMPOSITE SCORE (GRCS) AND COMPOSITE RESPONSE INDEX IN SSC(CRISS)

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Background: Systemic sclerosis (SSc) is a disease orphan of effective disease modifying agents. The diffuse cutaneous subset (dcSSc) is targeted in most clinical trials. Nevertheless, the high variability in clinical outcome at 12 months is limiting effective RCTs design and interpretation. The Global Ranked Composite Score (GRCS) and the Composite Response Index in SSc (CRISS) are the most recent attempts to capture overall response to treatment in dcSSc [1, 2]. Activation of interferon type 1 (IFN) pathway is associated with severe clinical manifestations in SSc. Several studies have indicated that the serum concentration of CCL2, CCL8, CCL19, CXCL9, CXCL10 and CXCL11 are the most relevant to measure IFN induced activation of PBMCs [3-4].

Objectives: Here we aimed to determine whether IFN pathway activation measured by a serum test could be used to stratify patients with dcSSc for severe clinical outcome at 12 months as measured by GRCS and CRISS.

Methods: Serum concentration of CCL2, CCL8, CCL19, CXCL9, CXCL10, and CXCL11 was measured by Luminex xMAP technology (Myriad RBM) in 143 SSc patients and 35 healthy controls (HC). IFN score was calculated as the average of the natural logarithm of the above chemokines. IFN score mean + 2STDV in the HC sera was adopted as cut off for IFN LO (within this range) or HI (above) [5]. Clinical outcomes at baseline and at 12 months were recorded. GRCS and CRISS were calculated at 12 months. GRCS were compared by Mann Whitney test. Fisher exact test was used to analyse the proportion of patients with CRISS of 0% or >0%. CRISS and GRCS correlation was tested by Spearman's rank correlation.

Results: All chemokines had a higher serum concentration in SSc vs HC (p<0.0001 for all). Median IFN score was higher in SSc than HC (5.26 vs 4.70, p<0.0001). There was no difference associated with disease subset or duration. To simulate enrollment criteria in a RCT we analyzed the 12 months outcomes of the dcSSc patients with ≤6 years disease duration. Sixty six 12-month outcome data were available. 37 were IFN HI and 29 IFN LO at baseline. The IFN HI group had a higher mRSS (median 9.5 vs 5, p=0.03), CRP (10.2 vs 5, p=0.0003) and NT-proBNP (195 vs 50.5, p=0.001). We recorded 7 deaths for SSc and 5 lung failures (3 FVC drop, 2 DLCO drop); 3 had worsening of FVC, 4 improvement and 49 no change; 11 had worsening of HAQ-DI, 5 improvement and 43 no change; 9 had worsening of mRSS, 7 improvement and 43 no change (table 1). GRCS ranged from -59 to 64 and was negative in 29 (21 IFN HI, 8 IFN LO) and positive in 37 (16 IFN HI, 21 IFN LO). IFN HI patients had a worse outcome at 12 months with GRCS median score of -12 vs 15 in IFN LO (p=0.0271)(fig. 1). Accordingly, GRCS favored IFN LO in 68.4% of 1073 (37*29) pairwise comparisons versus 31.6% of IFN HI (p=0.0001). CRISS was 0 in 46 (28 IFN HI, 18 IFN LO) and >0 in 20 (9 IFN HI, 11 IFN LO). Spearman's rank correlation of the two scores was r=0.5113. Consistent with GRCS data, CRISS was 0 in 76% of IFN HI vs 62% of IFN LO (P=0.046).

Conclusion: Serum IFN Score predicts worse clinical outcome at 12 months in dcSSc. Stratification for IFN score could aid both in clinical trial design and clinical management. Moreover, here we show that GRCS and CRISS may be sufficiently sensitive to measure difference in composite outcome at 12 months in dcSSc in an observational setting and they correlate with each other in this observational setting.

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Tab 1

Death		Organ Failure		FVC		HAQ		mRSS	
IFN HI	IFN LO	IFN HI	IFN LO	IFN HI	IFN LO	IFN HI	IFN LO	IFN HI	IFN LO
6	1	4	1	Worsening	1	2	7	4	8
				No change	26	23	23	20	23
				Improvement	2	2	1	4	3

Fig 1

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SERUM ANTI-MITOCHONDRIAL ANTIBODIES IN SYSTEMIC SCLEROSIS RECOGNIZE VARIABLE PYRUVATE DEHYDROGENASE COMPLEX ANTIGENS

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Background: Serum anti-mitochondrial antibodies (AMA) are the hallmark of primary biliary cholangitis (PBC) and are identified also in systemic sclerosis (SSc) patients with limited variant and serum anti-centromere antibodies (ACA). Indirect immunofluorescence (IIF) shows the cytoplasmic pattern that characterizes AMA positivity, but it is usually performed when a suspect of PBC is already present. Protein-immunoprecipitation (IP) and IP-Western Blot (WB) have the advantage of 1) identify AMA in an early screening phase, before the onset of PBC and liver function abnormalities; 2) detect the proteins that constitute the pyruvate dehydrogenase complex (PDC) complex (the subunits E1α, E1β, E2/E3, and E3BP) which seem to be associated to different risk of PBC onset.

Objectives: To determine the prevalence and clinical significance of the PDC complex subunits in AMA positive SSc patients with and without PBC.

Methods: Sera from 279 consecutive patients with rheumatic disease (146 with SSc, 77 with undifferentiated connective tissue disease -UCTD-, and 56 with polymyositis/dermatomyositis -PM/DM) were tested by protein-IP for the screening of serum autoantibodies. In 58/279 (21%) sera we report a complete or partial protein-IP pattern of 75-50-40-34kD bands corresponding to the 4 proteins of the PDC complex recognized by AMA. In these sera we performed IIF and IP-WB to confirm the identity of these bands, by using established protocols. Clinical charts were used to analyze clinical and laboratory data for possible statistical correlation.

Results: In 15/58 (26%) patients with protein-IP AMA pattern we confirm a diagnosis of PBC, and all of them had a diagnosis of SSc without additional rheumatic disease. Their expression of the PDC subunits is variable by IP-WB (Figure panel A), but this variability is not associated with specific clinical and laboratory features. In the 42/58 (72%) cases with AMA protein-IP pattern but without clinical and histological evidence of PBC, the E2 component of the PDC was detected in all except one patient, while the expression of the other proteins of the PDC was significantly less represented, i.e. E3BP in 14/42 (33%), E1β in 13/42 (31%), E3 in 6/42 (14%), and E1α in 4/42 (10%) patients. The IIF analysis on Hep2 cells of AMA positive samples also shows different patterns of expression, which spans from cytoplasmic positive staining with a reticular pattern in AMA positive sera for all the PDC proteins recognized by AMA, to cytoplasmic speckled pattern in cases with incomplete expression of PDC antigens (Figure panel B). So far, no specific clinical correlation was identified in these patients, as they did not have a diagnosis of