FRI0315

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%.

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	20
				Improvement	2	2	1	4	3

Fig 1

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FRI0316

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

PBC or other autoimmune liver disease or manifested elevated liver function tests.

Conclusion: The expression of the PDC antigenic components is variable both in SSc patients with AMA positive PBC and in SSc patients AMA positive without PBC or altered liver function tests, but we could not identify a clinical significance of this variability. It may be necessary to maintain a strict follow-up of these patients and to perform longitudinal studies to determine the prognostic value of this variable expression of PDC components in the onset of PBC.

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FRI0317

NOVEL CLASSIFICATION OF IDIOPATHIC INFLAMMATORY MYOPATHIES BASED ON DISTINCTIVE FEATURES AND AUTOANTIBODIES: ANALYSIS OF 67 KOREAN PATIENTS

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Background: Since Bohan and Peter first described their diagnostic criteria for idiopathic inflammatory myopathies (IIM) in 1975, new discoveries such as myositis-specific and myositis-associated autoantibodies (Abs) have been made.

Objectives: To investigate correlations between specific myositis Abs and their frequencies and clinical associations across different IIM groups, collectively demonstrating the utility of the new clinicoserologic classification in Korean adult patients with IIM.

Methods: We conducted a multicenter cohort study including 67 adult patients (age ≥ 18 years) who have been diagnosed as IIM by ENMC criteria. Immunoblot assay with Euroline strip (EUROIMMUN, Germany) was performed using the sera of definite dermatomyositis (DM, n=36), definite polymyositis (PM, n=25), amyopathic DM (n=4), DM sine dermatitis (n=1), and immune mediated necrotizing myopathy (IMNM, n=1). Patients were classified based on three classifications: 1) novel clinicoserologic classification suggested by Troyanov et al. in 2017. 2) 2017 EULAR/ACR classification criteria. 3) 2004 European neuromuscular center (ENMC) criteria. Associations of myositis Abs and clinical subsets of IIM were investigated.

Results: The distribution of the various IIM differed strikingly from those using the 3 classifications (Fig1). According to the 2004 ENMC classification and 2017 EULAR/ACR classification criteria, DM and PM was the most and the second frequent entities (DM: 55.2%, 56.7%; PM: 35.8%, 37.3%). But, using the new clinicoserologic classification, overlap myositis (OM) is the major type of IIM and the frequency of PM is significantly decreased. Anti-ARS Abs specificity included anti-Jo-1 (16.4%), -OJ (4.6%), -EJ (6.2%), -PL-7 (3.1%), and -PL-12 (4.6%). Interstitial lung disease was closely associated with anti-MDA5, and anti-ARS Abs, while DM-specific skin lesion was frequently observed in patients with anti-TIF1γ and anti-ARS Abs. Seven patients with cancer-associated DM were identified. They were positive for anti-TIF1γ (5/7) and anti-SRP (3/7) (table 1).

Table 3. Associations between myositis autoantibodies and distinctive clinical features

	Anti-ARS N=25	Anti-SRP N=24	Anti-MDA5 N=14	Anti-TIF1γ N=9	Anti-MG N=8	Anti-SAE N=3	Total N=87
ILD	20*	5	11*	0	3	1	36
Malignancy	1	3	0	5*	1	0	7
DM specific skin lesion	8*	6	10	9*	5	2	39
Dysphagia	2	2	2	3	2	1	16

*P<0.05, *P<0.001

Fig 1. Distribution of 67 patients according to 3 classifications for idiopathic inflammatory myopathies

Conclusion: Novel classification based on distinctive features and new myositis Abs reflects the clinical phenotype of IIM better. Establishment of a system routinely available to screen myositis Abs is needed. This will be beneficial to provide more precise diagnosis and proper management for patients with IIM.

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FRI0318

THROMBOCYTOPENIA AND MULTI-ORGAN INVOLVEMENT MIGHT BE POOR PROGNOSTIC FACTORS FOR SYSTEMIC SCLEROSIS CARDIOMYOPATHY

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Background: Systemic Sclerosis (SSc)-cardiomyopathy is associated with a high mortality in SSc. It is important to identify potential prognostic factors for SSc-cardiomyopathy.

Objectives: To describe the clinical characteristics and identify potential prognostic factors for patients with SSc-cardiomyopathy.

Methods: We retrospectively reviewed the clinical data of SSc-cardiomyopathy patients hospitalized at Sun Yat-Sen Memorial Hospital from January 1992 to November 2018. SSc-cardiomyopathy was defined as structurally and functionally abnormal of heart muscle in SSc patients with cardiac symptoms. Coronary artery disease, hypertension, valvular disease and congenital heart disease were excluded. The Chi-square test was used to compare the differences between the death group and the survival group.

Results:

1. There were 903 SSc patients recruited and 20 patients (2.2%) of them were SSc-cardiomyopathy. Among these 20 patients, 65% were females, age was 52.8±13.2 years, disease duration was 3.1±2.3 years, duration from SSc onset to cardiomyopathy occurred was 2.8±2.3 years.
2. SSc-cardiomyopathy developed in 18 patients (90%) with diffuse cutaneous SSc (dcSSc), and in 2 patients (10%) with limited cutaneous SSc (lcSSc). Eleven patients (55%) had pulmonary fibrosis, 7 patients (35%) had pulmonary arterial hypertension (PAH), 5 patients (25%) had scleroderma renal crisis (SRC) and esophageal involved respectively, 6