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POS0174 IMMUNOPHENOTYPE OF SJÖGREN'S SYNDROME AND SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS IDENTIFIED TWO ENDOTYPES WITH POTENTIAL THERAPEUTIC IMPLICATIONS

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Background: Primary Sjögren's syndrome (pSS) and systemic lupus erythematosus (SLE) are chronic autoimmune rheumatic diseases (ARDs) that share a strong female gender bias, as well as genetic, clinical and serological characteristics. Although significant progress has been made in improving treatment and patient related outcomes in pSS and SLE, there is a need for improved early diagnosis, adequate therapy monitoring, treatment of refractory manifestations and strategies to address co-morbidities. However, the results of many clinical trials are disappointing, and nobiologic treatments are licensed in pSS, while few are available for SLE patients with refractory disease.

Objectives: Identifying shared immunological features between patients with pSS and SLE that could lead to better treatment selection using a stratification approach.

Methods: Immune-phenotyping of 29 immune-cell subsets in peripheral blood from patients with pSS (n=45), SLE (n=29) and secondary SS associated with SLE (SLE/SS) (n=14) with low disease activity or in clinical remission, and sex-matched healthy controls (n=31), was performed using flow cytometry. Data were analysed using logistic regression and multiple t-tests and supervised machine learning (balanced random forest-BRF, sparse partial least squares discriminant analysis-sPLS-DA). Patients were stratified by k-means clustering. Clinical trajectories were analysed over 5 year follow-up.

Results: Comparing the immune profile of pSS and SLE patients using a variety of statistical and machine learning (ML) approaches, identified very few statistically significant differences between the two cohorts despite patients having a different clinical presentation and diagnosis. Thus, we hypothesised that immune-based subtypes could be shared between pSS, SLE and SLE/SS patients. Unsupervised k-means clustering was applied to the immunological features of the combined patient cohorts and two distinct patient endotypes, were identified: Group-1 (n=49; pSS=24, SLE=19, SLE/SS=6) and Group-2 (n=39; pSS=21, SLE=10, SLE/SS=8). Significant differences in immune-cell phenotypes across B-cell and T-cell subsets were identified by logistic regression, BRF (AUC=0.9942, assessed by 10-fold cross-validation) and sPLS-DA analysis. Comparison of the multiple analysis approaches identified eight common immune-cell subsets, including total and memory CD4+ and CD8+ T-cell subsets but no B-cell subsets. Using this common immune-signature the stratification between the groups was maintained and slightly improved (AUC=0.9979 and accuracy 96.16%). Interestingly, patients in Group-2 had elevated disease activity measures at baseline and over a 5-year trajectory compared to Group-1. Finally, correlation analysis identified correlations between disease activity markers and the top ranked immune features from the ML models.

Conclusion: The identified immune-cell signatures could reflect the underlying disease pathogenesis that spans diagnostic criteria and could be used to select patients for targeted therapeutic approaches.

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POS0175 ASSOCIATION BETWEEN BIOMARKERS AND THERAPEUTIC PATHWAY IN PATIENTS WITH SLE

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Background: SLE is heterogeneous in clinical presentation, underlying immunology, and response to therapy. Patients with severe or resistant disease receive cyclophosphamide or rituximab. Although effective, late use of these therapies entails cumulative damage.

Emerging predictors of response to rituximab include demographics, IFN-Scores and autoantibodies. For such predictors to change treatment strategy we need to understand their association with the effectiveness of other therapeutic options at earlier decision points.

Prospective studies of treatment pathways are difficult to perform, requiring large populations followed for many years. We therefore investigated this question by analysing retrospective treatment pathways since diagnosis in patients whose biomarker status is subsequently known.

Objectives: To use interferon scores and other markers to;

- [1] identify SLE patients more likely to need escalation of therapy to either rituximab or cyclophosphamide, and
- [2] determine if this occurred sooner than in others.

Methods: In patients with established SLE, attending Leeds SLE clinic, we collected demographics, clinical characteristics and blood at a single timepoint. Two previously validated IFN-Scores[1,2] (IFN-Score A and IFN-Score B) were measured using Taqman. Autoantibodies were measured using immunoprecipitation. Treatment history covering all antimalarials, oral and intravenous immunosuppressants (agent, start and stop dates and reasons) since diagnosis was collected. Univariable and multivariable Cox proportional hazards models were used to test variables as predictors of the primary endpoint: time to cyclophosphamide/rituximab.

Results: 124 patients were included. Follow up since diagnosis was Median (IQR) 37.5 (27.4-52.3) years, total therapies per patient was 3 (1-4), therapies per year was 0.2 (0.1-0.3). 54/124 (44%) patients required cyclophosphamide/rituximab.

Results of Cox regression are shown in the table 1. There was a significant association between high expression of IFN-Score B and requirement for cyclophosphamide/rituximab as well as trends for age in the first quartile (<28 years), IFN-Score A and anti-Sm/U1RNP antibodies. Both age <28 and IFN-Score B retained trends as independent predictors in a multivariable model.

Table 1.

Characteristic	CYC/ RTX=Yes n(%)	CYC/ RTX = No n(%)	Univariable Hazard ratio (95% CI)	Univariable p value	Multivariable Hazard Ratio (95% CI)	Multivariable p value
Age						
-Q1: under 28	22 (71%)	9 (29%)	2.25 (0.99,5.12)	0.054	1.74 (0.95,3.18)	0.074
-Q2: 28 – 38	12 (39%)	19 (61%)	1.03 (0.41,2.56)	0.949	Not included	Not included
-Q3: 38 – 52	12 (39%)	19 (61%)	1.52 (0.62,3.72)	0.360	Not included	Not included
-Q4: over 52	8 (26%)	23 (74%)	reference	reference	Not included	Not included
Ethnicity						
-Caucasian	42 (48%)	46 (52%)	1.17 (0.58,2.35)	0.660	Not included	Not included
-AfroCaribbean, South Asian, East Asian, Other	10 (36%)	18 (64%)	reference	reference		
IFN Score A, mean (SD)	-2.59 (-2.67)	-3.84 (-2.71)	1.10 (0.98,1.24)	0.113	Not included	Not included
IFN Score B, mean (SD)	-2.61 (-1.16)	-3.53 (-1.76)	1.31 (1.05,1.64)	0.017	1.23 (0.98,1.55)	0.079
Anti-Sm/U1RNP Ab positive	17 (61%)	11 (39%)	1.50 (0.84,2.67)	0.171	Not included	Not included
Anti-Ro(60) Ab positive	14 (45%)	17 (55%)	0.88 (0.47,1.65)	0.686	Not included	Not included