SLE, Sjögren's and APS - Clinical Aspects

OP0289

LLDAS (LOW LUPUS DISEASE ACTIVITY STATE), LOW DISEASE ACTIVITY (LDA) AND REMISSION (ON- OR OFF-TREATMENT) PREVENT DAMAGE ACCRUAL IN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) PATIENTS IN A MULTINATIONAL MULTICENTER COHORT

M. F. Ugarte-Gil^{1,2}, J. Hanly³, M. B. Urowitz⁴, C. Gordon⁵, S. C. Bae⁶, J. Romero-Diaz⁷, J. Sanchez-Guerrero⁷, S. Bernatsky⁸, A. E. Clarke⁹, D. J. Wallace¹⁰, D. Isenberg¹¹, A. Rahman¹¹, J. T. Merrill¹², P. Fortin¹³, D. D. Gladman⁴, I. N. Bruce¹⁴, M. A. Petri¹⁵, E. M. Ginzler¹⁶, M. A. Dooley¹⁷, R. Ramsey-Goldman¹⁸, S. Manzi¹⁹, A. Jonsen²⁰, R. Van Vollenhoven²¹, C. Aranow²², M. Mackay²², G. Ruiz-Irastorza²³, S. S. Lim²⁴, M. Inanc²⁵, K. C. Kalunian²⁶, S. Jacobsen²⁷, C. Peschken²⁸, D. L. Kamen²⁹, A. Askanase³⁰, B. Pons-Estel³¹, G. S. Alarcon^{32,33} on behalf of The SLICC Group. ¹Universidad Científica del Sur, School of Medicine, Lima, Peru; ²Hospital Nacional Guillermo Almenara Irgoyen, EsSalud, Rheumatology, Lima, Peru; ³Queen Elizabeth II Health Sciences Center and Dalhousie University, Department of Medicine and Department of Pathology, Nova Scotia, Canada; ⁴Toronto Western Hospital and University of Toronto, Center for Prognosis Studies in the Rheumatic Diseases, Ontario, Canada; ⁵University of Birmingham, Birmingham, Rheumatology Research Group, Institute of Inflammation and Ageing, College of Medical and Dental Sciences, Birmingham, United Kingdom; ⁶Hanyang University Hospital for Rheumatic Diseases, Rheumatology, Seoul, Korea, Rep. of (South Korea); ⁷Instituto Nacional de Ciencias Médicas y Nutrición, Immunología y Reumatología, Mexico City, Mexico; ⁸McGill University, Divisions of Rheumatology and Clinical Epidemiology, Quebec, Canada; ⁹Cumming School of Medicine, University of Calgary, Rheumatology, Alberta, Canada; ¹⁰UCLA, Cedars Sinai/David Geffen School of Medicine, Los Angeles, United States of America; ¹¹University College London, Medicine, London, United Kingdom; ¹²Oklahoma Medical Research Foundation, Department of Clinical Pathology, Oklahoma, United States of America; ¹³CHU de Québec - Université Laval, Rheumatology, Quebec, Canada; ¹⁴University of Manchester, Faculty of Biology Medicine and Health, Manchester Academic Health Sciences Center, Manchester, United Kingdom; ¹⁵Johns Hopkins University School of Medicine, Division of Rheumatology, Baltimore, United States of America; ¹⁶SUNY Downstate Medical Center, Department of Medicine, New York, United States of America; ¹⁷University of North Carolina, Thurston Arthritis Research Center, North Carolina, United States of America; ¹⁸Northwestern University and Feinberg School of Medicine, Medicine, Chicago, United States of America; ¹⁹Allegheny Health Network, Lupus Center of Excellence, Pennsylvania, United States of America; ²⁰Lund University, Department of Clinical Sciences Lund, Rheumatology, Lund, Sweden; ²¹Amsterdam UMC, Amsterdam University Medical Centers, Amsterdam, Netherlands; ²²Feinstein Institute for Medical Research, Feinstein Institute for Medical Research, New York, United States of America; ²³BioCruces Bizkaia Health Research Institute, Hospital Universitario Cruces, University of the Basque Country, Autoimmune Diseases Research Unit, Department of Internal Medicine, Barakaldo, Spain; ²⁴Emory University School of Medicine, Division of Rheumatology, Atlanta, United States of America; ²⁵Istanbul Medical Faculty, Istanbul University, Division of Rheumatology, Department of Internal Medicine, Istanbul, Turkey; ²⁶University of California San Diego, School of Medicine, La Jolla, United States of America; ²⁷Copenhagen University Hospital, Department of Rheumatology, Rigshospitalet, Copenhagen, Denmark; ²⁸University of Manitoba, Departments of Medicine and Community Health Sciences, Manitoba, Canada; ²⁹Medical University of South Carolina, Division of Rheumatology, Charleston, South Carolina, United States of America; ³⁰New York University, Hospital for Joint Diseases, New York, United States of America; ³¹Centro Regional de Enfermedades Autoinmunes y Reumáticas (GO-CREAR), Centro Regional de Enfermedades Autoinmunes y Reumáticas (GO-CREAR), Rosario, Argentina; ³²University of Alabama at Birmingham, Department of Medicine, Birmingham, Alabama, United States of America; ³³Universidad Peruana Cayetano Heredia, Facultad de Medicina, Lima, Peru

Background: Remission, LDA and LDAS have been proposed as treatment goals for SLE. However, the independent impact of these states on damage accrual has not been fully evaluated.

Objectives: To determine the independent impact of remission (both off & on treatment), LDA, and LLDAS on damage accrual.

Methods: We studied a long-term longitudinal multinational SLE cohort, including patients completing at least two annual assessments. Remission off-treatment was defined as a SLEDAI (excluding serology) = 0, without prednisone and immunosuppressive (IS) drugs. Remission on-treatment was defined as a SLEDAI (excluding serology) = 0, prednisone daily dose ≤ 5 mg/d and maintenance IS drugs. LDA was defined as a SLEDAI (excluding serology) ≤ 2, without prednisone or IS drugs. LLDAS was defined as a SLEDAI ≤ 4 with no activity in major organ systems, with no new features of lupus disease activity compared

to the previous assessment, prednisone daily dose ≤ 7.5 mg/d and maintenance IS drugs. Antimalarials were allowed in all groups. Damage accrual was ascertained with the SLICC/ACR damage index (SDI). Univariable and multivariable generalized estimated equation (GEE) negative binomial regression models were used. To create mutually exclusive groups, disease activity was divided into five states: remission off-treatment, remission on-treatment (minus remission off treatment), LDA (minus remission), LLDAS (minus remission and LDA) and not-optimally controlled. The proportion of the time that patients were in the specific state at each visit since cohort entry was determined. Possible effect modifiers and confounders adjusted for included sex, age at diagnosis, race/ethnicity, education, baseline disease duration, follow-up time, the highest-ever glucocorticoid dose prior to cohort entry, antimalarials and SDI. Time-dependent covariates were determined at the same annual visit as disease activity state; the outcome was the increase in the SDI and it was assessed at the subsequent visit.

Results: There were 1,652 patients, 1464 (88.6%) were female, mean age at diagnosis was 34.6 (SD 13.4) years and mean baseline disease duration was 5.5 (SD 4.1) months. Patients had a mean follow-up of 6.5 (SD 4.3) years, 11686 visits were included. 763 patients (46.2%) had an increase in SDI score ≥ 1 during follow-up. 2483 (21.2%) of the visits were classified as remission off-treatment, 2276 (19.5%) as remission on-treatment, 544 (4.7%) as LDA, 657 (5.6%) as LLDAS and 5726 (49.0%) as not-optimally controlled. Being in remission off-treatment, remission on-treatment, LDA and LLDAS were predictive of a lower probability of damage accrual [remission off-treatment IRR=0.403, 95% CI 0.301-0.541; remission on-treatment IRR=0.313 (95% CI 0.218-0.451) LDA: IRR=0.469 (CI 95% CI 0.272-0.809); LLDAS IRR=0.440 (95% CI 0.241-0.803)]. The multivariable model is summarized in Table 1.

Table 1. Multivariable GEE model of the impact of disease activity states on damage accrual.

	Incidence Rate Ratio	95% CI
Disease activity state		
Remission off treatment	0.403	0.301-0.541
Remission on treatment	0.313	0.218-0.451
LDA	0.469	0.272-0.809
LLDAS	0.440	0.241-0.803
Gender, male	1.274	1.086-1.495
Age at diagnosis	1.024	1.020-1.029
Ethnicity		
Caucasian US	Ref.	
Caucasian other	1.017	0.849-1.217
African	1.467	1.211-1.776
Asian	0.863	0.693-1.075
Hispanic	1.266	1.034-1.550
Other	1.121	0.759-1.656
Educational level, years	0.977	0.957-0.996
Disease duration at baseline	0.960	0.801-1.150
Follow-up time	0.942	0.923-0.960
Antimalarial use	0.786	0.681-0.908
Highest prednisone dose before baseline	1.002	1.001-1.007
SDI before	1.100	1.050-1.1152

LLDAS: Low lupus disease activity state LDA: Low disease activity SDI: SLICC/ACR Damage Index

Conclusion: Remission on- and off-treatment, LDA and LLDAS were associated with less damage accrual, even adjusting for possible confounders and effect modifiers. This highlights the importance of treating to target in SLE.

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OP0290

CLINICAL CHARACTERISTICS AND PROGNOSIS OF ANTIPHOSPHOLIPID SYNDROME PATIENTS BASED ON CLUSTER ANALYSIS: A 10-YEAR COHORT STUDY

W. Qi¹, J. L. Zhao¹, X. Tian¹, M. Li¹, X. Zeng¹. ¹Peking Union Medical College Hospital, Department of Rheumatology, Beijing, China

Background: APS is an autoimmune disease characterized by persistent antiphospholipid antibodies (aPLs) positivity, leading to thrombotic events or pregnancy morbidity. High-risk aPLs profiles included positive lupus anticoagulant (LA) and multiple aPLs positivity¹. Association was also found between aPLs and a variety of manifestations beyond thrombosis, referred to "non-criteria manifestations" (i.e. thrombocytopenia, hemolytic anemia, heart valve disease and aPL-related nephropathy)², of which the role in APS risk stratification is poorly understood. The manifestation spectrum of APS is wide, ranging from asymptomatic aPLs positivity to life-threatening catastrophic APS, and patients other than confirmed APS also need proper management. Therefore, a risk stratification integrating demographic data, aPL-related manifestations, aPLs profiles, coexisting cardiovascular risk factors and SLE is needed for management guidance and prognosis assessment.

Objectives: Using cluster analysis, to identify phenotypes among aPL-positive patients and assess the prognosis of each phenotype.

Methods: This is a single-center, prospective cohort study of aPL-positive patients who presented to Peking Union Medical College Hospital from 2004 to 2020. Demographic characteristics, aPL-related manifestations, cardiovascular risk factors, antibodies profile and follow-up data were recorded. The primary end point was defined as a combination of newly onset arterial thrombosis (AT) or deep venous thrombosis (DVT), major bleeding events, non-criteria manifestations and all-cause death. Hierarchical cluster analysis with the Euclidean distance and the Ward method was applied to identify clusters of patients and variables separately. Multiple comparison and Kaplan-Meier survival analysis were performed among clusters.

Results: Four clusters among 383 patients (70.2% female; mean age 37.7 years) were identified (Figure 1A). Cluster 1 (n=138): female patients with SLE, non-criteria manifestations, triple aPLs positivity, high AT rate and moderate DVT rate. Cluster 2 (n=112): male patients with obesity, smoking history, hypertension, hyperhomocysteinemia, triple aPLs positivity and the highest rate of AT and DVT. Cluster 3 (n=83): female patients with the highest pregnancy morbidity rate and the lowest thrombosis rate. Cluster 4 (n=50): 62% male patients with isolated LA positivity, high AT rate and moderate DVT rate. Four clusters of variables were also identified (Figure 1A). From Kaplan-Meier survival analysis, 1-, 5- and 10-year event-free survival rates were 92.6%, 79.8% and 66.8%, respectively. Cluster 3 showed lowest incidence of primary endpoint (Figure 1B), while Cluster 1 and 2 showed higher newly-onset AT risk compared with other clusters (P=0.028 for 2 vs 3 and P=0.049 for 2 vs 4).

Figure 1.

Conclusion: We identified 4 clinical phenotypes of aPL-positive patients. APS secondary to SLE was always aggregated with non-criteria manifestations. Clinicians should be alert to the possibility of SLE in aPL-positive patients with coexisting non-criteria manifestations, for whom immunosuppressive therapy besides anticoagulation may be necessary. Cluster 4 represented patients with isolated LA positivity and shared similar prognosis with secondary APS and male patients, which confirmed that LA represented a high-risk antibody spectrum. Additionally, cardiovascular risk factors (i.e. male, smoking history and obesity) played an important role in thrombosis events, and led to poor prognosis.

Therefore, more attention should be paid to male patients, and the screening and management of cardiovascular risk factors should not be ignored.

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OP0291

SEVERITY OF LABIAL MINOR SALIVARY GLAND FOCUS SCORE AND FUTURE LYMPHOMA DEVELOPMENT IN SJÖGREN'S SYNDROME

A. Goules¹, L. Chatzis¹, V. Pezoulas², C. Baldini³, F. Skopouli⁴, A. Venetsanopoulou⁵, P. Voulgaris⁶, S. De Vita⁶, M. Voulgarelis¹, H. M. Moutsopoulos⁷, D. Fotiadis², A. Tzioufas¹. ¹School of Medicine, National and Kapodistrian University of Athens, Pathophysiology, Athens, Greece; ²University of Ioannina, Unit of Medical Technology and Intelligent Information Systems, Athens, Greece; ³University of Pisa, Rheumatology Unit, Department of Clinical and Experimental Medicine, Athens, Greece; ⁴Harokopio University of Athens, Department of Nutrition and Clinical Dietetics, Athens, Greece; ⁵University of Ioannina, Department of Internal Medicine, Athens, Greece; ⁶University of Udine, Rheumatology Clinic, Department of Medical area, Athens, Greece; ⁷Academy of Athens, Chair Medical Sciences/Immunology, Greece, Athens, Greece

Background: The typical histologic picture of focal sialadenitis in the labial minor salivary gland (LMSG) tissues has been incorporated as a parameter in the majority of Sjögren's syndrome (SS) classification criteria, with focus score (FS) being the most widely used (1). In previous studies, higher FS has been associated with the presence of autoantibodies and extra-glandular manifestations including lymphoma, implying that FS can predict severe disease (2,3). However, there are no studies exploring the association of FS with lymphoma development along with the time interval from SS diagnosis to lymphoma diagnosis.

Objectives: To investigate an association of focus score grading with lymphoma development and time to lymphoma occurrence.

Methods: From a total population 1998 consecutive patients fulfilling the 2016 ACR-EULAR criteria for SS who were followed-up in 5 Rheumatology centers from Greece and Italy (Universities of Athens, Pisa, Udine, Harokopio and Ioannina) (UPAH group), those with positive (LMSG) (FS ≥ 1) were identified. (1). Patients who had not been subjected to an LMSG biopsy or had a negative biopsy (FS < 1) or the biopsy was evaluated using other histologic classifications were excluded from the present study. Lymphoma patients with diagnostic LMSG biopsy performed within a year from lymphoma diagnosis as well as non-lymphoma patients with less than 1 year between SS diagnosis and their last follow up, were also excluded. Cumulative clinical and histologic data attributed to SS as defined by ESSDAI and/or ESSPRI, up to lymphoma diagnosis or last follow up, were recorded. A combined data driven Fast Correlation Based Feature selection (FCBF)/Logistic Regression (LR) model was applied on the unified dataset to identify independent lymphoma associated risk factors. A correlation between FS and time interval until lymphoma diagnosis was performed using the Pearson formula.

Results: A unified dataset of 618 SS patients with FS ≥ 1 and at least one year of disease duration from SS diagnosis to lymphoma diagnosis or last follow up, with 30 clinical, laboratory and histologic features, was constructed. The median age at SS diagnosis was 53 (range: 15 – 80) years old, the female to male ratio was 20:1 and the median disease duration was 6 years (range: 1-35). Half (49%) of the study population had focus score between one and two (1 ≤ FS < 2), followed by a declining proportion of patients accounted for every subsequent escalating FS group. No statistically significant difference was found regarding disease duration among the various FS escalating groups (p=0.1603, Kruskal-Wallis test). Fifty eight patients had lymphoma with no statistically significant difference in disease duration compared to non-lymphoma controls. The data driven FCBF/LR algorithm with lymphoma on the whole dataset revealed that cryoglobulinemia (p=0.021), salivary gland enlargement (p=0.008) and FS (p=0.049) are independent lymphoma associated risk factors. A statistically significant negative correlation was found using a Pearson formula (R=-0.32 and p=0.015) regarding the focus score and the time to lymphoma diagnosis.

Conclusion: This is the largest study of SS patients' histologic analysis exploring the association of LMSG FS grading with lymphoma development and the time interval until its diagnosis. Higher FS values correlate with increased lymphoma risk and early lymphoma occurrence.