POS0106

BILAG-2004 LDA AND BST LDA ARE VALID TREAT TO TARGET IN SLE

C. S. Yee¹, C. Gordon², M. Akil³, P. Lanyon⁴, C. J. Edwards⁵, D. Isenberg⁶, A. Rahman⁶, L. S. Teh⁷, S. Tosounidou⁸, R. Stevens¹, A. Prabu², B. Griffiths⁹, N. Mchugh¹⁰, I. N. Bruce¹¹, Y. Ahmad¹², M. Khamashta¹³, V. Farewell¹⁴ on behalf of British Isle Lupus Assessment Group (BILAG). ¹Doncaster & Bassetlaw Teaching Hospitals NHS Foundation Trust, Department of Rheumatology, Doncaster, United Kingdom; ²University of Birmingham, Rheumatology Research Group, Birmingham, United Kingdom; ³Sheffield Teaching Hospitals NHS Foundation Trust, Department of Rheumatology, Sheffield, United Kingdom; ⁴Nottingham University Hospitals NHS Trust, Department of Rheumatology, Nottingham, United Kingdom; ⁵University Hospital Southampton NHS Foundation Trust, Department of Rheumatology, Southampton, United Kingdom; ⁶University College London, Centre for Rheumatology Research, London, United Kingdom; ⁷Royal Blackburn Hospital, Department of Rheumatology, Blackburn, United Kingdom; ⁸Sandwell and West Birmingham Hospitals NHS Trust, Department of Rheumatology, Birmingham, United Kingdom; ⁹Newcastle upon Tyne Hospitals NHS Foundation Trust, Department of Rheumatology, Newcastle, United Kingdom; ¹⁰Royal National Hospital for Rheumatic Diseases NHS Trust, Department of Rheumatology, Bath, United Kingdom; ¹¹The University of Manchester, Centre for Epidemiology Versus Arthritis, Manchester, United Kingdom; ¹²Betsi Cadwaldr University Health Board, Department of Rheumatology, Wales, United Kingdom; ¹³Guy's and St Thomas' NHS Foundation Trust, Department of Rheumatology, London, United Kingdom; ¹⁴University of Cambridge, MRC Biostatistics Unit, Cambridge, United Kingdom

Background: Low disease activity state has been defined using SLEDAI and used as treatment target in SLE. However, there has not been any such definition using BILAG-2004 index (BILAG-2004).

Objectives: This study was to determine if low disease activity state according to BILAG-2004 is valid for use as treatment target in SLE. We also assessed disease activity longitudinally using BILAG-2004 systems tally (BST). BST is an alternative way of representing BILAG-2004 scores that combines the flexibility and simplification of numerical scoring of BILAG-2004 with the clinical intuitiveness of BILAG-2004 structure.

Methods: This was a prospective multi-centre longitudinal study in the UK of an inception cohort of SLE patients (recruited within 12 months of achieving 1997 ACR revised criteria for SLE). Data were collected on disease activity (BILAG-2004 and BILAG2004-Pregnancy Index during pregnancy), SLICC/ACR DI (SDI), cumulative drug exposure and death at every visit. This study ran from 1st January 2005 to 31st December 2017. Four low disease activity states (LDA) were defined using BILAG-2004: 1) BILAG-2004 LDA when all 9 systems had scores of C, D or E on assessment (no Grade A or B), 2) BST LDA when there was persistent score of C, D or E in all 9 systems between 2 consecutive visits (equivalent to 2 consecutive visits with BILAG-2004 LDA), 3) BILAG-2004 Remission when all 9 systems had scores of D or E on assessment and 4) Persistent Remission when there was persistent score of D or E in all 9 systems between 2 consecutive visits. Longitudinal analysis using Poisson regression with random effects model was used with development of new damage as the outcome of interest. Gender, cardiovascular risk factors, antiphospholipid syndrome status and most drugs (except hydroxychloroquine, glucocorticoids, mycophenolate and cyclophosphamide) were excluded from the model as they were not associated with development of damage in univariate analysis.

Results: 273 patients were recruited (91.2% female, 59.3% Caucasian, 17.2% African/Caribbean, 17.2% South Asian) with mean age at recruitment of 38.5 years (SD 14.8). 97.8% had no damage at recruitment (2.2% had SDI score of 1). Median follow-up was 73.4 months (range: 1.8, 153.8) with total follow-up of 1767 patient-years. There were 13 deaths and 114 new damage items occurred during follow-up. There were 6674 assessments with disease activity score: 319 assessments with Grade A activity in 95 patients (84.6% had only 1 system with grade A, range: 1 - 4) and 1704 assessments with Grade A or B activity in 239 patients (78.7% had only 1 system with Grade A or B, range: 1 - 5).

BILAG-2004 LDA was achieved in 74.5% of assessments (from 271 patients). BILAG-2004 Remission occurred in 28.2% of assessments (from 234 patients). 6401 observations with BST were available (1 observation derived from change in activity between 2 consecutive assessments) and 63.7% were in BST LDA. There was no observation with Persistent Remission between consecutive visits. Table 1 summarises multivariate analysis which showed BILAG-2004 LDA to be inversely associated with damage. Similar results were obtained with BILAG-2004 Remission (RR 0.60 with 95% CI 0.38, 0.96) and BST LDA (RR 0.65 with 95% CI 0.43, 0.99). Cumulative drug exposure since recruitment for mycophenolate was protective against new damage (RR 0.99 with 95% CI 0.99, 0.99).

Table 1.

Variable	Relative Risk (95% CI) for New Damage
Ethnicity	
Afro-Caribbean	1.22 (0.68, 2.18)
South Asian	1.81 (0.97, 3.38)
Others	2.22 (0.63, 7.85)
Age at diagnosis	1.06 (1.04, 1.08)
Prior SDI score	0.68 (0.43, 1.06)
BILAG-2004 LDA	0.60 (0.39, 0.94)
Hydroxychloroquine since last visit (per g)	0.99 (0.98, 0.99)
Steroids since last visit (per 100mg)	1.02 (1.01, 1.03)
Cyclophosphamide since last visit (per g)	1.67 (1.15, 2.41)

Conclusion: BILAG-2004 LDA and BST LDA are valid treatment targets in SLE. BILAG-2004 Remission and Persistent Remission are uncommon, which make them unrealistic as a treatment target.

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POS0107

TAPERING BELIMUMAB IN PATIENTS WITH SLE: A SINGLE CENTER EXPERIENCE

M. Fredi¹, T. Vojinovic², F. Regola¹, G. Babaglionis³, D. Bettoni³, I. Cavazzana², F. Franceschini¹. ¹UO Reumatologia e Immunologia Clinica ASST Spedali Civili e Università degli Studi di Brescia, ASST Spedali Civili, Brescia, Italy; ²UO Reumatologia e Immunologia Clinica, ASST Spedali Civili, Brescia, Italy; ³Farmacia Aziendale, ASST Spedali Civili, Brescia, Italy

Background: In Italy, the use of belimumab has been authorized since 2013, in patients with active systemic lupus erythematosus (SLE) with positive anti-double-stranded DNA and low C3 or C4 levels, despite standard therapy. Belimumab is effective in reducing disease activity and number of flares and in blocking damage progression. To our knowledge, no data are available on dose tapering of belimumab in SLE patients chronically treated with it.

Objectives: The aim of this retrospective study was to analyse prevalence of tapering in a single cohort and to evaluate disease activity after tapering.

Methods: Patients, who received intravenous belimumab (10mg/kg) for at least 12 months between June 2013 and December 2020 were enrolled. The Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC-SDI), Physician Global Assessment (PGA), C3 and C4 levels, and prednisone daily dose were recorded at baseline and every six-months. Follow-up was stopped when patients switched to subcutaneous belimumab or when it was discontinued for more than 6 months (interrupted). Dose tapering was defined as the prolongation of the regular dose interval, after initial treatment based on the registered dosage.

Results: Between June 2013 and December 2020, 48 patients received intravenous belimumab for at least 12 months (100% Caucasians, 94% females). All patients received standard belimumab dosage of 10mg/Kg every 4 weeks. Fourteen (29.1%) of 48 patients lengthened the dosing interval to 5 weeks; a subsequent lengthening of the interval occurred in 7 patients every 6 weeks and in 1 patient belimumab was gradually tapered to every 13 weeks.

Twelve months (T12) after belimumab introduction, 3 patients (6.2%) were receiving a tapered dosage; at T24, 9 out of the 37 (24.3%), at T36 9 out of 21 (42.8%), and at T48 8 out of 18 (44.4%). Differences in disease activity, damage, concomitant medications, disease duration at belimumab introduction (baseline) were evaluated among patients that maintained the standard interval versus the group that received a tapered dose. Notably, no differences were found among the two groups (standard dose vs tapering) concerning median age at baseline (41, IQR 31-47.5 vs 38, IQR 32.2-51.5), disease duration (median 11, IQR 7.2-16

vs 9, IQR 5.5-14.5), median prednisone daily dosage (7.1mg, IQR 5-11.9 versus 11mg, IQR 7.6-17.5) and median SLEDAI-2K (8, IQR 6-9.75 vs 8, IQR 5-10). Differences in concomitant medications or clinical manifestations are reported in Figure 1A.

Among the group that received the standard dose, 7 patients discontinued the treatment (20.6%), specifically 2 renal flares and one adverse event occurred. Whereas, in the reduced dose group, 2 discontinuations occurred (14.3%) due to a pregnancy and a renal flare. Noteworthy, the patient with the renal flare resumed subcutaneous belimumab 12 months after the flare. Finally, the disease activity was analysed in the 12 months after the first drug reduction (Figure 1B-E), with no sign of worsening of evaluated parameters (Figure 1B-1E), but with a significant reduction of steroids and SLEDAI-2K, 6 months after tapering.

Conclusion: In our single retrospective cohort, we have demonstrated that belimumab tapering seems to be safe and not associated with a worsening disease activity over the following months. However, further studies are required to identify eligibility criteria and to determine the optimal dose-tapering strategy both for the intravenous and the subcutaneous formulations.

Figure 1.

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POS0108 PLASMA MITOCHONDRIAL DNA AS A BIOMARKER IN DIAGNOSIS AND FOLLOW-UP OF SYSTEMIC LUPUS ERYTHEMATOSUS

S. Giaglis^{1,2}, D. Daoudarian^{1,2}, D. Kyburz^{1,2}, N. Venhoff³, U. Walker^{1,2}.

¹University of Basel, Department of Biomedicine, Laboratory for Experimental Rheumatology, Basel, Switzerland; ²University Hospital Basel, Department of Rheumatology, Basel, Switzerland; ³University Medical Center Freiburg, Department of Rheumatology and Clinical Immunology, Freiburg, Germany

Background: A fundamental role of mitochondria in systemic lupus erythematosus (SLE) was recently demonstrated (1). In brief, mitochondrial ROS participate in the formation of neutrophil extracellular traps (NETs) (2), while extrusion of cell-free mitochondria and highly oxidized interferogenic mtDNA causes disease in an animal model of SLE (3-5).

Objectives: The diagnostic and prognostic value of cell-free DNA in SLE is still unknown. The aim of the present study was therefore to examine the clinical utility of cell-free DNA quantification as a non-invasive biomarker in SLE.

Methods: Total DNA was isolated from platelet-free plasma samples of healthy individuals (HC) and consecutive SLE patients. Plasma and clinical data were collected at baseline and follow-up. Copy numbers were quantified by qPCR for mitochondrial (mt) DNA (ATP-6 gene) and nuclear (n) DNA (GAPDH gene).

Results: Fifty-six HC (median age 48.3 ± 13.5, 64% female) and 103 SLE patients (median age 46.8 ± 15.8, 99% female, mean SLEDAI: 3 ± 4) were available for analysis.

mtDNA levels were significantly elevated in SLE plasma (1.3x10⁸ copies/ml plasma, 95% CI: 7.3x10⁷ to 1.7 x10⁸), compared to HC plasma (8.6x10⁶ copies/ml plasma, 95% CI: 6.9x10⁶ to 1.0x10⁷, p<0.0001). nDNA levels in contrast did not differ between SLE (8.3x10⁶ copies/ml plasma, 95%CI: 5.9x10⁶ to 1.4 x10⁷) and HC (1.0x10⁷ copies/ml plasma, 95%CI: 2.0x10⁶ to 1.5 x10⁷, p=0.61). Receiver operating characteristic curve analysis showed that a cut-off value of 1.9x10⁷ mtDNA copy numbers differentiated between SLE and HC with 87.4% sensitivity, 94.6% specificity and an AUC of 0.95 (Figure 1a).

mtDNA levels correlated with the SLE Disease Activity Index 2000 (SLEDAI-2K) (r=0.29, p=0.0026), less so also nDNA copy numbers (r=0.24, p=0.014). There was no association of mtDNA elevation with any particular type of SLE organ involvement and no correlation between mtDNA copy numbers in SLE plasma and dsDNA antibody levels.

Follow-up data were available for 32 SLE patients (median follow-up 4.0 months, IQR: 4.0). delta mtDNA-levels robustly correlated with changes in SLEDAI-2K (r=0.51, p=0.0012, Figure 1b).

Conclusion: The quantification of cell free mtDNA, but not nDNA copy numbers allows a sensitive and specific distinction between healthy individuals and patients with SLE. mtDNA levels correlate cross sectionally with disease activity in SLE patients and within individual SLE patients longitudinally with the SLEDAI. Plasma mtDNA quantification may therefore aid in the diagnosis of SLE and in monitoring SLE activity.

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Figure 1. (a) Receiver operating characteristic curve for mtDNA plasma concentrations to discriminate between HC and SLE patients. AUC: area under the curve. (b) Changes in plasma mtDNA levels in SLE patients correlate with the evolution of disease activity at follow-up.

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POS0109 IDENTIFICATION OF PRIMARY SJOGREN'S SYNDROME SUBTYPES BY MACHINE LEARNING

M. T. Qiu^{1,2,3}, S. X. Zhang^{1,2,3}, J. Qiao^{1,2,3}, J. Q. Zhang^{1,2,3}, S. Song^{1,2,3}, R. Zhao^{1,2,3}, M. J. Chang^{1,2,3}, Y. Zhang^{1,2,3}, G. Y. Liu¹, P. F. He⁴, X. Li^{1,2,3}. ¹The Second Hospital of Shanxi Medical University, Department of Rheumatology, Taiyuan, China; ²Shanxi Li Xiaofeng Medical Groups, Department of Rheumatology, Taiyuan, China; ³Ministry of Education, Key Laboratory of Cellular Physiology at Shanxi Medical University, Taiyuan, China; ⁴Shanxi Medical University, Medical Data Sciences, Taiyuan, China

Background: Sjogren's syndrome (pSS) is a chronic, progressive, and systematic autoimmune disease characterized by lymphocytic infiltration of exocrine glands ^{1,2}. Sicca symptoms and abnormal fatigue are the main clinical presentation, but those symptoms are non-specific to patients, which lead to delayed diagnosis ^{1,3}. The heterogeneous of clinical manifestation raise challenges regarding diagnosis and therapy in pSS, thus it's necessary for us to sub-classify pSS.

Objectives: To explore new biomarkers for diagnosis and subtypes of pSS based on Machine Learning Primary.

Methods: All microarray raw data (CEL files) were screened and downloaded from Gene Expression Omnibus (GEO). Meta-analysis to identify the consistent DEGs by MetaOmics. Weighted gene co-expression network analysis (WGCNA) was used to the modules related to SS for further analysis. Subclasses were computed using a consensus Non-negative Matrix Factorization (NMF) clustering method. Immune cell infiltration was used to evaluate the expression of immune cells and obtain various immune cell proportions from samples. P value < 0.05 were considered statistically significant. All the analyses were conducted under R environment (version 4.03).

Results: A total of 3715 consistent DEGs were identified from the four datasets, including 1748 up-regulated and 1967 down-regulated genes. Tour