LSO-075 PERFORMANCE OF CONVENTIONAL CARDIOVASCULAR RISK SCORES IN IDENTIFYING SUBCLINICAL ATHEROSCLEROSIS IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Background Cardiovascular disease (CVD) is a major cause of mortality in systemic lupus erythematosus (SLE). Role of conventional risk scores which look at cardiovascular events, in assessing subclinical atherosclerosis in SLE is not fully established. This study aims to assess performance of QRESEARCH database risk score-3 (QRISK3), systemic coronary risk evaluation (SCORE) and WHO (World Health Organization) CVD scores in subclinical atherosclerosis and determine clinical associations of the same.

Methods This is a single center cross-sectional analytical study which enrolled 79 patients with SLE (without CVD) and 76 healthy controls. Demography, disease activity, autoantibodies, steroid dose were noted. Subclinical atherosclerosis (carotid plaque or abnormal carotid intima media thickness cIMT) and CVD risk (QRISK3, SCORE and WHO scores) were assessed. Agreement between scores was determined using kappa coefficient.

Results Subclinical atherosclerosis was seen in 52% SLE (abnormal cIMT-47% and plaque- 8%) and 53% healthy controls (abnormal cIMT-47% and plaque 12%). Mean age of cohort was 45±6 years, mean SLE duration 96±64 months, SLEDAI 1 ±2.3 and median SLICC ACR DI of 1 (0–2). SCORE, WHO and QRISK3 had sensitivity of 0%, 10% and 28% in detecting subclinical atherosclerosis in SLE, 20%, 22% and 5% in controls while specificity was 0%, 82% and 79% in SLE and 97%, 91% and 100% in controls respectively. Kappa agreement was 0 for SCORE with other scores, between QRISK3 and WHO 68% and 15% for plaque in SLE and controls, 31% for cIMT in SLE and controls respectively. Anticardiolipin IgG (14.6% vs 2.6%) was numerically higher in SLE with atherosclerosis but not statistically significant.

Conclusions Sensitivity of conventional CVD scores in detecting subclinical atherosclerosis was very poor in SLE with QRISK3 and WHO score having good specificity. Hence, until further scores are validated, screening for subclinical atherosclerosis using carotid ultrasound remains gold standard.

LSO-106 RISK FACTORS ASSOCIATED WITH THE DEVELOPMENT OF CARDIOVASCULAR EVENTS IN A MULTIETHNIC ASIAN SYSTEMIC LUPUS ERYTHEMATOSUS COHORT

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Background Objective: To determine the risk factors associated with the development of cardiovascular events (CVE) in a multi-ethnic Asian cohort of Singapore Systemic Lupus Erythematosus (SLE) patients

Methods We analysed patients in a prospective SLE cohort Tock Seng Hospital (TTSH) in Singapore during the period 2002 to 2017. Patients without prior CVE at baseline visit (V0) who subsequently developed CVE during the follow-up were identified from this registry. Clinical information on traditional, SLE-associated, and treatment-associated risk factors were collected at baseline and at follow up. Predictors associated with development of CVE were analyzed using Chi-squared test and student's t test.

Results Out of 1000 patients recruited, 132 were excluded due to prior CVE before V0 and/or withdrew consent. Of the remaining 868 patients, 42 (4.8%) developed a CVE (16 angina/acute myocardial infarction/ischaemic heart disease, 17 cerebrovascular accidents, 11 arterial thrombosis/peripheral vascular disease) after a median (Interquartile range IQR) time of 6.18 (2.70 – 9.13) years. Of those who developed CVE, the median (IQR) age of SLE diagnosis was 34.75 (25.89 – 44.95) years and median (IQR) SLE duration was 10.66 (4.31 – 15.45) years before CVE onset. The risk factors for development of CVE ($p<0.05$) include onset of SLE at an older age, longer disease duration, longer exposure to corticosteroids, less usage of hydroxychloroquine, presence of hypertension, hyperlipidemia, antiphospholipid syndrome and lower creatinine clearance at time of enrolment into the study.

Conclusions Besides traditional risk factors, age, disease duration and corticosteroid use are predictors of CVE in this prospective study. The use of hydroxychloroquine appear to be protective.

LSO-107 ASSOCIATION OF HYPERTENSION WITH HIGHER CHRONICITY INDEX SCORES AMONG PATIENTS WITH LUPUS NEPHRITIS

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Background Kidney biopsies provide useful information to guide management in lupus nephritis (LN). Standard histopathology report includes ISN/RPS class, as well as Activity Index (AI) and Chronicity Index (CI) scores representing inflammation and fibrosis, respectively. We analyzed the clinical attributes associated with histopathologic class, AI and CI scores in patients with LN.

Methods We reviewed the medical records of LN patients seen at the University of Santo Tomas (UST, Manila Philippines) who underwent kidney biopsies from 2015 to 2022. Correlations between SLE disease characteristics at time of biopsy with ISN/RPS class, AI and CI scores were analyzed using Pearson correlation coefficient.

Results Of 44 patients (95.5% females), 13 and 29 patients had Class III and Class IV LN respectively, 1 each with co-existing Class V. Two patients had pure Class V, there were no patients in the other classes. Mean age was 25.1±10.3 years at LN diagnosis, with average disease duration of 2.4 ±3.7 years from diagnosis to biopsy. 70.5% had mild to moderate disease (SLEDAI<12) at biopsy. Average serum creatinine was 1.4±0.87 mg/dL, eGFR 71.8±37.7 mL/min, UPCR 2.6±1.4, and SLEDAI 10.6±4.4. Of renal parameters, only hypertension was associated with higher CI ($r=0.417$, $p=0.002$); although there was a trend for higher UPCR ($r=0.144$,$p=0.176$) and serum creatinine ($r=0.221$,$p=0.075$)

correlating with higher AI, this was not statistically significant. Extra-renal features of oral ulcers (r=-0.368,p=0.007), arthritis (r=-0.461,p=0.001), and serositis (r=-0.301, p=0.023) were associated with lower CI scores. There was no correlation of individual disease parameters with ISN/RPS class.

Conclusions This study demonstrated a significant correlation of hypertension with higher chronicity index scores among LN patients. Extra-renal disease activity features of oral ulcers, arthritis and serositis had lower CI scores. Aside from early aggressive management of active LN, strict sustained blood pressure control must be reinforced throughout the disease course in order to prevent renal damage.

Short oral presentation session 14: SLE precision medicine

LSO-076 UNDERSTANDING THE GENETIC ARCHITECTURE OF SLE FROM THE PERSPECTIVE OF ASSOCIATIONS FROM 14 OTHER AUTOIMMUNE DISEASES

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Background Genetic factors play key roles in the pathogenesis of systemic lupus erythematosus (SLE). In the last one and half decade, genome-wide association studies (GWAS) have seen enormous successes, revealing nearly 200 associated loci. However, for large number of loci, the causal variant(s), the association mechanism(s) are unclear. For some, the target gene(s) are unknown or controversial. Lack of functional understanding is the major challenge for translating genetic findings into clinical applications.

Methods In this study, we compared the association signals for SLE with the associations from 14 other autoimmune diseases, using linkage disequilibrium and conditional analyses to identify the shared and specific association signals. We annotated these signals using genomic resources such as eQTL, histone marks, chromatin accessibility, TF binding, and promoter interaction. Relevant cell types and signaling networks are constructed and compared among these diseases.

Results Analyzing the association signals between SLE and other autoimmune diseases and genomic annotations allow us to have a better grip on the causal genes and association mechanisms. Specific associations are identified for SLE even when the locus is shared with other diseases, including in IKZF1, ETS1, IL12A, DUSP22, IL12RB2, and CD40. Specific target genes, distinct cell types and signaling networks are detected for SLE. The differences suggested by these analyses raise intriguing questions on the shared and unique mechanisms of these autoimmune diseases.

Conclusions Genetic analysis and genomic annotations of associated loci for SLE in comparison with associations with 14 other autoimmune diseases facilitate the identification of the causal genes and the association mechanisms for SLE. The signals that are shared, or SLE-specific, or lack thereof shed new light on this prototype autoimmune disease from different angles.

LSO-077 IDENTIFICATION OF AN INTERFERON 5-GENE SIGNATURE SCORE AS A PHARMACODYNAMIC AND POTENTIAL PREDICTIVE BIOMARKER FOR DEUCRAVACITINIB TREATMENT IN A PHASE 2 TRIAL IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Background Tyrosine kinase 2 (TYK2) mediates cytokine pathways (eg, Type I IFN) linked with SLE pathogenesis. Deucravacitinib is a first-in-class, oral, selective, allosteric TYK2 inhibitor approved for the treatment of adults with plaque psoriasis.[1 2] Deucravacitinib was efficacious in a phase 2 SLE trial.[3] We developed a customized IFN 5-gene signature score, assessed the pharmacodynamic effects of deucravacitinib on the IFN score, and evaluated the score's association with SLE disease activity and clinical response in the phase 2 trial.

Methods Patients were randomized equally to placebo or deucravacitinib (3 mg BID, 6 mg BID, or 12 mg QD). DxTerity chemical ligation-dependent probe amplification was used to measure 51 immune system-related genes from whole blood. IFN genes were selected based on distribution, correlations, hierarchical clustering, and consistency of k-means clusters. Serum proteins, blood cell subsets, and antibodies were measured by immunoassays and flow cytometry. SRI(4) and BICLA were measured at weeks 32 and 48.

Results An IFN 5-gene (MX1, HERC5, IFIT1, RSAD2, and EIF2AK2) signature score was identified and used to classify patients into IFN-high or IFN-low subgroups (figure 1). Higher baseline score was associated with higher baseline SLEDAI and CLASI scores, higher IFN activity biomarker (eg, IFNα, IFNλ, BAFF, CXCL10) and anti-dsDNA levels, and lower complement and lymphocyte counts. Baseline score was not predictive of SRI(4) response. A higher baseline score was associated with a significantly higher probability of BICLA response with deucravacitinib 3 mg BID relative to placebo (P=0.014). Deucravacitinib reduced the score from weeks 4 through 44 by >50%.

Conclusions These data support the IFN 5-gene signature score as a biomarker to classify patients with SLE into IFN-high or IFN-low subgroups; however, clinical response by IFN score was inconsistently improved (table 1). IFN-regulated gene expression performs well as a pharmacodynamic biomarker to confirm deucravacitinib mechanism of action and to aid in phase 3 dose selection.