INVESTIGATION ON THE EFFECT AND MECHANISM OF ABNORMALLY ACTIVATED CD8+ T CELLS FROM BONE MARROW ON HEMATOPOIETIC STEM CELLS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Background: SLE is an autoimmune disease characterized by the abnormal function of lymphocytes. The impairment of hematopoietic function of bone marrow participates in its pathogenesis, in which T cells play an important role. However, study on bone marrow T cells in SLE patients is very limited.

Objectives: This study aims to characterize the phenotype and molecular characteristics of abnormally activated CD8+ T cells in bone marrow of SLE patients and explore the mechanism of hematopoietic stem cells (HSCs) reduction caused by the abnormally activated CD8+ T cells in bone marrow of patients with SLE.

Methods: A total of 8 SLE patients and 5 age- and sex-matched controls were recruited in our study. Among them, 3 SLE patients and 4 donors were collected blood samples of bone marrow. The peripheral blood samples for Single-cell RNA-sequencing (scRNA-seq) and functional studies. BM and peripheral T cell subsets were measured by flow cytometry. Plasma cytokines and secreted immunoglobulins were detected by Luminex. Disease activity of SLE patients was measured using the SLE Disease Activity Index (SLEDAI). All analyses were performed using R language and Flowjo 9.

Results: In the present study, SLE patients had increased CD8+ TIL and decreased CD4+ TIL/T cells in bone marrow of SLE, compared to healthy controls. A large number of CD38+HLADR+CD8+ T cells existed in the bone marrow and peripheral blood of SLE patients. These patients also showed reduced numbers of HSCs, and with a downward trend of the numbers of peripheral red blood cells, white blood cells, neutrophils, hemoglobin, and platelets. By scRNA-seq, the CD38+HLADR+CD8+ T cells contained high levels of GZMK, GZMA, PRF1, IFNG, and TNF in the bone marrow of SLE patients. The CD38+HLADR+CD8+ T cells exhibited significant relationship with HSCs, white blood cells, neutrophils, and platelets.

Conclusion: These findings demonstrated that the abnormally activated CD8+ T cells in bone marrow can reduce the number of HSCs by the expression of killer molecules, which contributes to the impairment of hematopoietic function and the development of SLE. This project focuses on the specific bone marrow T cell subset in SLE. The completion of this project provides information for exploring the mechanism of hematopoiesis involvement.

REFERENCES:

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CAN THE SLE-DAS SUBSTITUTE BILAG TO MEASURE LUPUS DISEASE ACTIVITY IN CLINICAL TRIALS? POST-HOC ANALYSIS OF THE BLISS-76 TRIAL

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Background: The primary endpoint for randomized clinical trials (RCT) in Systemic lupus erythematosus (SLE) is usually defined as proportionate responders in a composite index. The most widely used are British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA) and Systemic Lupus Responder Index (SRI). Both comprise BILAG along with SLE Disease Activity Index (SLEDAI). BICLA and SRI are complex and time-consuming to assess. The SLE Disease Activity Score (SLE-DAS) is an easy to apply, validated continuous disease activity measure, highly correlated with SLEDAI, with higher accuracy and sensitivity-to-change as compared to SLEDAI.

We hypothesize that SLE-DAS can also identify the SLE disease activity information from BILAG, thus dispensing the use of composite indexes for RCT.

Objectives: To compare the ability of the SLE-DAS and the Safety of Estrogens in Lupus National Assessment (SELENA)-SLEDAI to discriminate between BILAG classification of mild vs. moderate vs. severe disease activity.

Methods: Post-hoc analysis of all intention-to-treat patients in the BLISS-76 (NCT00410384) RCT at the baseline study visit. SELENA-SLEDAI and BILAG were assessed at time of the study visits and SLE-DAS was retrospectively scored from the study database. Patients' disease activity was classified as: (i) mild (no BILAG B or A scores in any organ domain); (ii) moderate (1 BILAG B, no A scores); (iii) severe (>2 BILAG B and/or ≥1 BILAG A). Ability of the SLE-DAS and SELENA-SLEDAI to differentiate between: (i) mild vs. moderate/severe disease activity; (ii) mild/moderate vs. severe disease activity (according to BILAG), were evaluated using receiver operating characteristic (ROC) analysis. The area under the ROC curves (AUCs) with 95% confidence intervals (95% CI) as a measure of discriminatory ability of the SLE-DAS and SELENA-SLEDAI, were compared using Delong's test for two correlated curves. Because AUC measurements might have restricted accuracy for imbalanced datasets, precision-recall (PR) curves and area under PR curves (AUC-PR) were also performed. Statistical significance was set at 0.05.

Results: We included 819 patients, classified by BILAG as presenting mild (77%), moderate (28.8%) or severe (63.5%) disease activity. To differentiate mild vs. moderate/severe disease activity, the discriminatory ability of SLE-DAS was outstanding (AUC 0.948; 95% CI 0.923-0.973), while that of SELENA-SLEDAI was acceptable (AUC 0.729; 95% CI 0.657-0.801) (figure 1A). To differentiate mild/moderate vs. severe disease activity, the discriminatory ability of SLE-DAS was excellent (AUC 0.873; 95% CI 0.846-0.899), while that of SELENA-SLEDAI was acceptable (AUC 0.707; 95% CI 0.670-0.744) (p<0.005) (figure 1B). The AUC-PR confirmed the higher performance of SLE-DAS over SELENA-SLEDAI to differentiate mild vs. moderate/severe disease activity (0.995 vs. 0.965, respectively) (figure 1C) and mild/moderate vs. severe disease activity (0.902 vs. 0.794, respectively) (figure 1D).

Conclusion: The SLE-DAS presents excellent performance in assessing SLE disease activity categorized by BILAG scores, which is not the case for SELENA-SLEDAI. Further studies will aim to better define ability of SLE-DAS to substitute composite responder indexes.

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The new ACR/EULAR 2019 criteria showed a 99.4% sensitivity and 89.1% specificity in the case group, and 62.6% of patients presented ANA+, 8.6% hypocomplementemia, and 1.3% positive Antiphospholipid antibodies. The most frequent diseases were Rheumatoid Arthritis (46.1%), Scleroderma (18.1%), Systemic Lupus Erythematosus (18.1%), and 3.8% in the control group.

Results:
The ACR/EULAR 2019 criteria for SLE were estimated with Spearman correlation test. STATA 15.0 was used for data analysis. Descriptive statistics was estimated. Sensitivity, specificity, positive and negative LR of the criteria and the correlation of their global score with activity and damage indexes of the disease were recorded. In addition, activity and damage indexes were recorded in the group with SLE.

Three SLE experts, blinded to the diagnosis determined, had a lower risk of experiencing a flare (OR=0.23 and 0.46 respectively). Similarly, reproductive health and pregnancy counselling adherence was associated with reduced risk for adverse outcomes during the last year of observation (OR 0.97, 95% CI 0.95-0.99) respectively. Success in monitoring QIs was associated with reduced glucocorticoids, and 92% the recommended hydroxychloroquine dose. Dependence-related QIs. Regarding targets of therapy, sustained remission or low disease activity and damage indexes were estimated with Spearman correlation test. STATA 15.0 was used for data analysis.

Results: A total of 365 patients from 7 centres in Argentina were included. A One hundred and eighty-three belonged to the SLE group: 92.3% women, mean age 39 years (SD 13.3), median disease duration 92 months (IQR 37-150). The most frequent manifestations of the disease were mucocutaneous (94%), musculoskeletal (82.5%) and haematological (69%). All patients presented ANA+, 88% hypocomplementemia, 69.4% Anti-DNA and 19.5% antiphospholipid antibodies. Median SLEDAI and SLICC were 2 (IQR 0-6) and 0 (IQR 0-1), respectively.

In the control group, 182 patients were recruited: 84% women, mean age 53.6 years (SD 14.2) and median disease duration 82.5 months (IQR 38-151). The most frequent diseases were Rheumatoid Arthritis (46.1%), Scleroderma (18.1%) and Sjögren’s syndrome (5%) and most common manifestations were musculoskeletal (81.9%), immunological (73.6%) and constitutional (25.3%). A total of 62.6% of patients presented ANA+, 8.6% hypocomplementemia, and 13% Antiphospholipid antibodies.

Ninety-one percent of patients in the case group were classified as defined SLE and 3.8% in the control group.

The ACR/EULAR 2019 Criteria showed a 99.4% sensitivity and an 89.1% specificity, with a LR+ of 9.1 and 0.007, respectively. The sensitivity and specificity of SLICC 2012 criteria were 98.3% and 88%, respectively with a LR+ of 8.2 and a LR- of 0.02; and the ACR 1997 criteria showed a 93.96% sensitivity and 90.1% specificity, with LR+ of 8.21 and LR- of 0.07.

The correlations between the ACR/EULAR 2019 Criteria global score, and activity and damage indexes were 0.19 and -0.036, respectively.

Conclusion: The new ACR / EULAR 2019 criteria have shown high sensitivity, a specificity comparable to its predecessors, and a higher ability to distinguish SLE from other diseases and to exclude it in non-SLE patients. No correlation was observed between the criteria scores and activity and damage indexes.