ORAL ABSTRACT PRESENTATIONS

O007 / #176

Topic: ***AS24 - SLE-Treatment***

ABSTRACT CONCURRENT SESSION 01: FINDINGS FROM LUPUS CLINICAL TRIALS
22-05-2025 1:40 PM - 2:40 PM

EFFICACY AND SAFETY OF ELSUBRUTINIB AND UPADACITINIB COMBINATION AND UPADACITINIB MONOTHERAPY FOR THE TREATMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS: RESULTS THROUGH 104 WEEKS

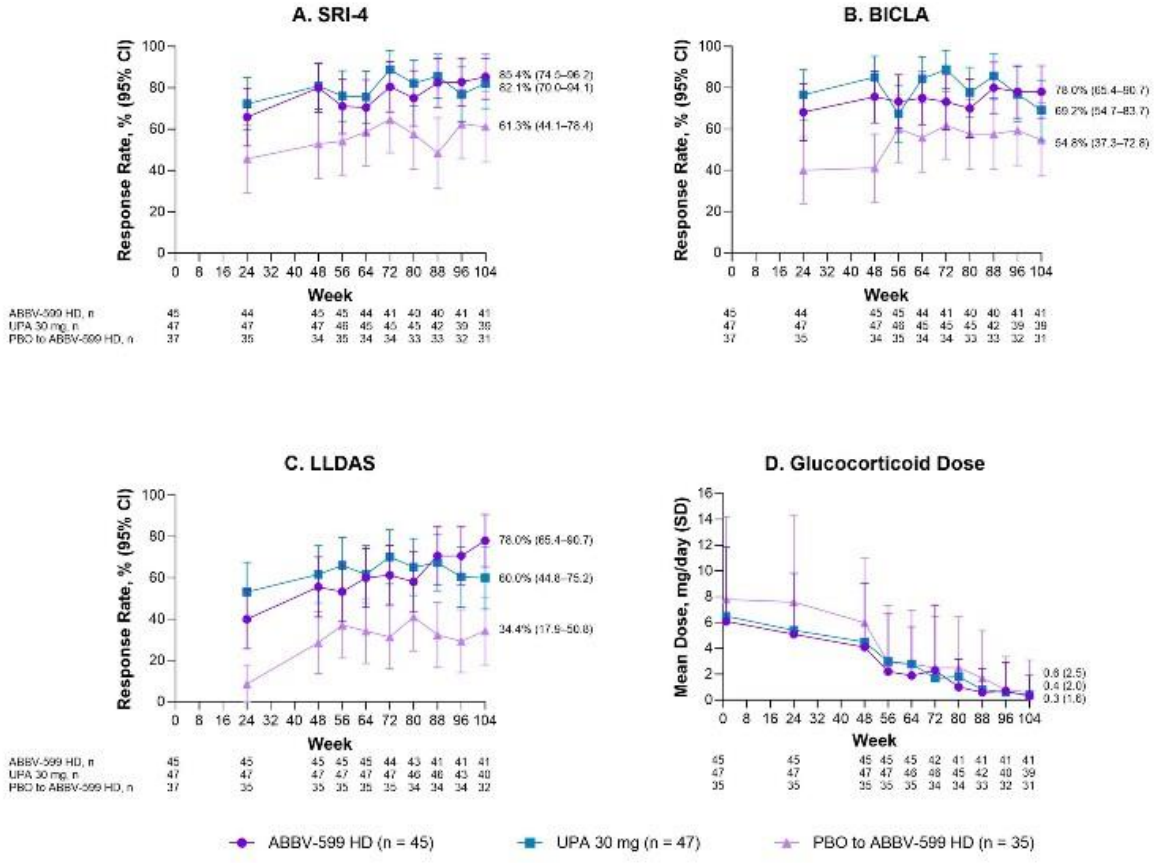
Kristin D'Silva[1], Joan . Merrill[2], Amit Saxena[3], Martin Aringer[4], Yoshiya Tanaka[5], Xiaofeng Zeng[6], Ling Cheng[1], Thao Doan[1], Shelly Kafka[1], David D'Cruz[7]
[1]AbbVie, North Chicago, United States of America, [2]Oklahoma Medical Research Foundation, Clinical Immunology Program, Oklahoma City, United States of America, [3]NYU Langone Health, Division Of Rheumatology, New York, United States of America, [4]University Medical Center and Faculty of Medicine, Dresden, Germany, [5]University of Occupational and Environmental Health Japan, The First Department Of Internal Medicine, Kitakyushu, Japan, [6]Peking Union Medical College Hospital, Rheumatology, Beijing, China, [7]Guy's and St Thomas' Hospitals NHS Foundation Trust, London, United Kingdom

Background/Purpose: ABBV-599 (a combination of a selective Bruton's tyrosine kinase inhibitor, elsubrutinib [ELS], and a selective Janus kinase inhibitor, upadacitinib [UPA]) targets a spectrum of signaling pathways associated with SLE, which may extend the immunologic effects of either alone. In the phase 2 SLEek study (NCT03978520), patients with moderately to severely active SLE were randomized 1:1:1:1:1 to receive once daily ABBV-599 high dose (HD; ELS 60 mg + UPA 30 mg), ABBV-599 low dose (LD; ELS 60 mg + UPA 15 mg), ELS 60 mg, UPA 30 mg, or placebo (PBO). After a planned interim analysis, the ABBV-599 LD and ELS 60 mg groups were discontinued due to lack of efficacy. Through 48 weeks, treatment with ABBV-599 HD or UPA 30 mg resulted in significant improvements in SLE disease activity and flares compared with PBO. Here, we report results from the SLEek long-term extension (LTE) study (NCT04451772) through 104 weeks.

Methods: In the LTE study, patients continued their original randomized treatment from the SLEek study except for the PBO group, who were rerandomized 1:1 to ABBV-599 HD or ABBV-599 LD at week 48. This analysis included the continued groups: ABBV-599 HD, UPA 30 mg, and PBO to ABBV-599 HD. Efficacy measures included SLE Responder Index (SRI-4), BILAG–based Combined Lupus Assessment (BICLA), Lupus Low Disease Activity State (LLDAS), mean glucocorticoid dose, and flares. Treatment-emergent adverse events (TEAEs) were summarized using the Medical Dictionary for Regulatory Activities v26.0. Efficacy (as observed) and safety were assessed through 104 weeks.

Results: The LTE included 127 patients (ABBV-599 HD, n = 45; UPA 30 mg, n = 47; PBO to ABBV-599 HD, n = 35). Baseline characteristics were balanced across groups. The proportion of patients achieving SRI-4 increased from weeks 48 through 104 to 85.4% (95% CI, 74.5–96.2), 82.1% (95% CI, 70.0–94.1), and 61.3% (95% CI, 44.1–78.4) in the ABBV-599 HD, UPA 30 mg, and PBO to ABBV-599 HD groups, respectively (**Figure 1**). Other secondary endpoints (BICLA and LLDAS) were either maintained or improved through week 104 in the ABBV-599 HD and UPA 30 mg groups and improved from weeks 48 through 104 in the PBO to ABBV-599 HD group. In all 3 groups, patients were nearly glucocorticoid free by week 104. TEAEs occurred in 75.6%, 66.0%, and 85.7% of patients in the ABBV-599 HD, UPA 30 mg, and PBO to ABBV-599 HD groups, respectively (**Table**). No cases of venous thromboembolism or major adverse cardiovascular events occurred.

Figure 1. Key Efficacy Endpoints Through Week 104 of Achievement of (A) SRI-4, (B) BICLA, (C) LLDAS, and (D) Change From Baseline in Daily Glucocorticoid Dose



ABBV-599 HD, ABBV-599 high dose (elsubrutinib 60 mg + UPA 30 mg); BICLA, British Isles Lupus Assessment Group–based Composite Lupus Assessment; LLDAS, Lupus Low Disease Activity State; PBO, placebo; SRI-4, SLE Responder Index-4; UPA, upadacitinib.

All available measurements were used for analysis, and there was no imputation for missing values.

Table. Treatment-Emergent Adverse Events From Weeks 48 Through 104

	ABBV-599 HD (n = 45) n (%)	UPA 30 mg (n = 47) n (%)	PBO→ABBV-599 HD (n = 35) n (%)
Summary of TEAEs			
Any TEAE	34 (75.6)	31 (66.0)	30 (85.7)
COVID-19–related TEAEs	9 (20.0)	12 (25.5)	6 (17.1)
TEAEs considered possibly related to study drug by the investigator	13 (28.9)	8 (17.0)	13 (37.1)
Severe TEAEs	5 (11.1)	4 (8.5)	5 (14.3)
Serious TEAEs	5 (11.1)	5 (10.6)	1 (2.9)
TEAEs leading to discontinuation of study drug	3 (6.7)	2 (4.3)	2 (5.7)
Deaths due to TEAEs	0	0	0
TEAEs of Special Interest			
Serious infections	1 (2.2)	4 (8.5)	0
Opportunistic infection excluding tuberculosis and herpes zoster	0	1 (2.1)[a]	0
Herpes zoster	2 (4.4)	1 (2.1)	3 (8.6)
Active tuberculosis	0	0	0
Malignancy	1 (2.2)	0	0
Malignancies excluding NMSC	0	0	0
NMSC	1 (2.2)[b]	0	0
Adjudicated GI perforations	0	0	0
Adjudicated MACE[c]	0	0	0
Anemia	2 (4.4)	0	0
Neutropenia	1 (2.2)	0	1 (2.9)
Lymphopenia	2 (4.4)	0	0
Renal dysfunction	0	0	0
Hepatic disorders	3 (6.7)	1 (2.1)	2 (5.7)
Adjudicated VTE[d]	0	0	0

ABBV-599 HD, ABBV-599 high dose (elsubrutinib 60 mg + UPA 30 mg); ELS, elsubrutinib; GI, gastrointestinal; MACE, major adverse cardiovascular event; NMSC, nonmelanoma skin cancer; TEAE, treatment-emergent adverse event; UPA, upadacitinib; VTE, venous thromboembolism.

[a]Non-serious event of cytomegalovirus chorioretinitis. [b]One subject experienced NMSC, which was excised and resolved. The event was considered unrelated to study drug by the investigator [c]MACE defined as cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. [d]VTE defined as deep vein thrombosis and pulmonary embolism (fatal and nonfatal).

Conclusions: In patients with moderately to severely active SLE, ABBV-599 HD or UPA 30 mg resulted in maintenance or further improvement in lowered disease activity, flare reduction, and decreased glucocorticoid use through 104 weeks of treatment. Patients who switched from PBO to ABBV-599 HD at week 48 improved in all measures through week 104. No new safety signals were identified.

O008 / #335

Topic: ***AS24 - SLE-Treatment***

ABSTRACT CONCURRENT SESSION 01: FINDINGS FROM LUPUS CLINICAL TRIALS
22-05-2025 1:40 PM - 2:40 PM

DOSE-DEPENDENT EFFICACY AND SAFETY OF LOW-DOSE IL-2 IN THE TREATMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS

Jing He, Xia Zhang, Ruiling Feng, Haihong Yao, Zhanguo Li
Peking university people's hospital, Beijing, China

Background/Purpose: Interleukin-2 (IL-2) has shown potential in immune modulation for autoimmune diseases, esp. systemic lupus erythematosus (SLE). This study investigates the dose-dependent （at different dose levels） efficacy and safety of IL-2 in patients with active SLE, aiming to determine the optimal dose for balancing therapeutic efficacy with tolerability.

Methods: In this multicenter, randomized, double-blind, placebo-controlled phase IIb study, we enrolled SLE patients who were randomized (1:1:1:1) to receive IL-2 at doses of 0.2M, 0.5M, or 1M IU, or placebo for 12 weeks, followed by weekly the same dosing for another 12 weeks. The primary endpoint was the SLE Responder Index-4 (SRI-4) at week 24, with secondary endpoints assessing Treg expansion, safety, and clinical parameters across different dose groups.

Results: Between Septemper 2019 and July 2024, a total of 152 patients were randomized in a 1:1:1:1 ratio to receive IL-2 at different doses: 0.2M IU (n=38), 0.5M IU (n=38), 1M IU (n=37), or placebo (n=39). At week 24, SRI-4 response rates were 87.9%, 79.4%, and 62.9% for the 1 million IU, 0.5 million IU, and 0.2 million IU groups, respectively, compared to 44.1% for placebo (**Fig.1A and B**). Significantly higher patients achieved Lupus Low Disease Activity State (LLDAS) and improvements in Physician's Global Assessment (PGA) scores were also observed (**Fig.1D and E**). Secondary end points with respect to mucocutaneous, musculoskeletal, and hematological involvement also showed a significant benefit with Ld-IL2. Patients in 1M IU exhibited significant expansion of Treg cells and reduced glucocorticoid usage, compared to lower doses and placebo (**Fig.1F**). The safety profile across all IL-2 groups was favorable with fewer infection complications reported, including upper respiratory tract infection and urinary tract infection. At week 24, the 1M IU IL2 group showed significantly more patients achieving improvement than the placebo group

Conclusions: This study demonstrated a dose-dependent response with Ld-IL2 in reducing disease activity in SLE, particularly with the 1 million IU dose, which showed optimal clinical and immunological benefits.

O009 / #367

Topic: ***AS24 - SLE-Treatment***

ABSTRACT CONCURRENT SESSION 01: FINDINGS FROM LUPUS CLINICAL TRIALS
22-05-2025 1:40 PM - 2:40 PM

IMPROVEMENTS OBSERVED IN SKIN AND JOINT MANIFESTATIONS OF SYSTEMIC LUPUS ERYTHEMATOSUS WITH DAPIROLIZUMAB PEGOL TREATMENT: RESULTS FROM A PHASE 3 TRIAL

Anca Askanase[1], Ann Clarke[2], Dafna D Gladman[3], Victoria P. Werth[4], Md Yuzaiful Md Yusof[5], Janine Gaiha-Rohrbach[6], Teri Jimenez[7], E. Dietlind Koch[8], Ágnes Koncz[9], Annette Nelde[10], Ronald Van Vollenhoven[11]
[1]Columbia University Medical Center, New York, United States of America, [2]Division of Rheumatology, Department of Medicine, University of Calgary, Calgary, Canada, [3]Krembil Research Institute, Toronto Western Hospital, Toronto, Canada, [4]Department of Dermatology, Hospital of the University of Pennsylvania and Philadelphia PVAMC, Philadelphia, United States of America, [5]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, and National Institute for Health and Care Research Leeds Biomedical Research Centre, Leeds, United Kingdom, [6]Biogen, Cambridge, United States of America, [7]UCB, Raleigh, United States of America, [8]UCB, Monheim, Germany, [9]UCB, Brussels, Belgium, [10]Biogen, Baar, Switzerland, [11]Department of Rheumatology, Amsterdam University Medical Centre, Amsterdam, Netherlands

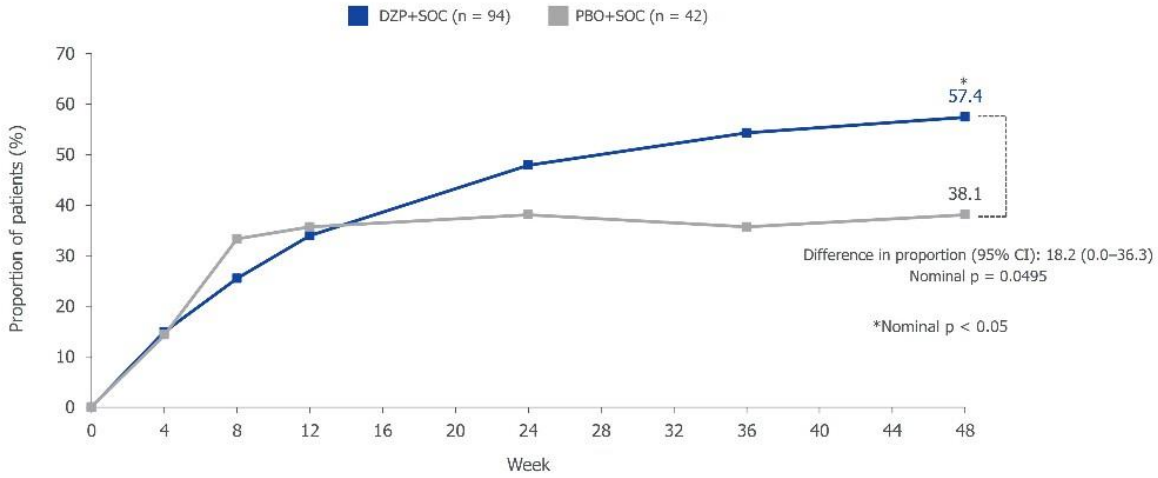
Background/Purpose: Dapirolizumab pegol (DZP) is a novel, polyethylene glycol (PEG)-conjugated antigen-binding (Fab') fragment, lacking an Fc domain, that inhibits CD40L signaling. In the phase 3 PHOENYCS GO trial (NCT04294667) in patients with systemic lupus erythematosus (SLE), DZP resulted in improvements in different global disease activity endpoints at Week 48 vs placebo (PBO), and was generally well tolerated.[1] Here, we report the impact of DZP on SLE skin and joint manifestations in patients in the PHOENYCS GO trial.

Methods: PHOENYCS GO was a 48-week, randomized, double-blind, PBO-controlled trial. Patients aged ≥ 16 years with moderate-to-severe, active SLE characterized by persistently active or frequently flaring/relapsing-remitting disease activity despite stable standard of care (SOC) medication (antimalarials, corticosteroids, and/or immunosuppressants) were included. Patients were randomized 2:1 to intravenous DZP 24 mg/kg plus SOC medication (DZP+SOC) or PBO+SOC every 4 weeks. Cutaneous Lupus Disease Area and Severity Index (CLASI) and tender/swollen joint counts (TJC/SJC) were recorded at baseline and Weeks 4, 8, 12, 24, 36, and 48. The proportion of patients achieving meaningful improvement in CLASI Activity (CLASI-A) Score (≥ 50% improvement) in all patients and those with high CLASI-A Score (≥ 8) at baseline, and

the proportion with a meaningful decrease in TJC/SJC (≥ 50% decrease) are reported. Difference in proportion responding between DZP+SOC and PBO+SOC, 95% CIs, and p values were estimated and tested using the Cochran-Mantel-Haenszel (CMH) risk difference estimate controlling for stratification factors. Analyses were performed on the full analysis set.

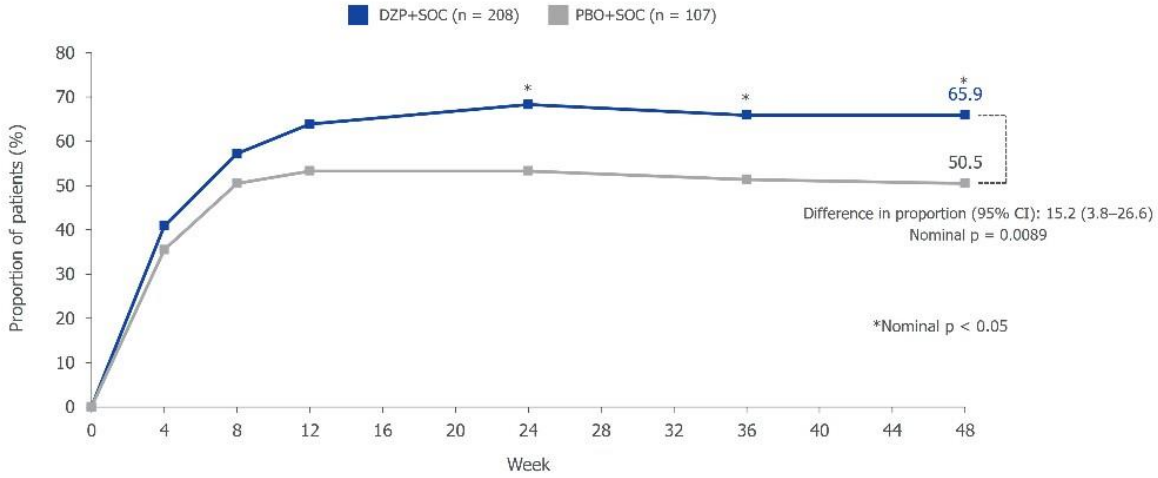
Results: At baseline, mean (SD) CLASI-A Score was similar between patients receiving DZP+SOC (8.0 [5.7]; n = 208) and PBO+SOC (7.8 [6.8]; n = 107). Overall, 97.1% (202/208) receiving DZP+SOC and 93.5% (100/107) receiving PBO+SOC had CLASI-A Score > 0 at baseline. Additionally, 45.2% (94/208) and 39.3% (42/107) receiving DZP+SOC and PBO+SOC had CLASI-A Score ≥ 8 at baseline. Of all patients, 57.2% (119/208) vs 39.3% (42/107) receiving DZP+SOC vs PBO+SOC achieved ≥ 50% improvement in CLASI-A Score at Week 48 (nominal p = 0.0022; difference 17.7%). Among those with CLASI-A Score ≥ 8 at baseline, 57.4% (54/94) vs 38.1% (16/42) receiving DZP+SOC vs PBO+SOC achieved ≥ 50% improvement at Week 48 (nominal p = 0.0495; difference 18.2%; achievement over time is shown in **Figure 1**). At baseline, mean (SD) TJC was 11.7 (6.7) and 11.8 (7.5), and SJC was 7.9 (5.2) and 7.2 (5.7), in patients receiving DZP+SOC (n = 208) and PBO+SOC (n = 107), respectively. The mean (SD) number of joints which were tender and swollen (T&SJC) at baseline was 7.4 (5.0) and 6.8 (5.6) in patients receiving DZP+SOC and PBO+SOC. After 48 weeks, 65.9% (137/208) vs 50.5% (54/107) of all patients receiving DZP+SOC vs PBO+SOC achieved ≥ 50% decrease in T&SJC (nominal p = 0.0089; difference 15.2%; achievement over time is shown in **Figure 2**). Similar results at Week 48 were achieved for TJC only (63.5% vs 44.9%; nominal p = 0.0014; difference 18.4%) and SJC only (65.4% vs 49.5%; nominal p = 0.0078; difference 15.6%).

Figure 1. Achievement of ≥ 50% improvement in CLASI-A Score over time in patients with CLASI-A Score ≥ 8 at baseline (NRI)



Full analysis set. *Nominal p < 0.05 for the DZP+SOC vs PBO+SOC comparison. Difference in proportion responding between DZP+SOC and PBO+SOC, 95% CIs for difference in proportions, and p values were estimated and tested using the Cochran-Mantel-Haenszel (CMH) risk difference estimate controlling for stratification factors. CI: confidence interval; CMH: Cochran-Mantel-Haenszel; CLASI-A: Cutaneous Lupus Disease Area and Severity Index Activity; DZP: dapirolizumab pegol; NRI: non-responder imputation; PBO: placebo; SOC: standard of care.

Figure 2. Achievement of ≥ 50% decrease in T&SJC over time in all patients (NRI)



Full analysis set. *Nominal p < 0.05 for the DZP+SOC vs PBO+SOC comparison. Difference in proportion responding between DZP+SOC and PBO+SOC, 95% CIs for difference in proportions, and p values were estimated and tested using the Cochran-Mantel-Haenszel (CMH) risk difference estimate controlling for stratification factors. CI: confidence interval; CMH: Cochran-Mantel-Haenszel; DZP: dapirolizumab pegol; NRI: non-responder imputation; PBO: placebo; SOC: standard of care; T&SJC: tender and swollen joint count.

Conclusions: Beyond the previously reported significant improvement in overall disease activity,[1] treatment with DZP+SOC resulted in meaningful improvements in both skin and joint manifestations in patients with SLE. **References:** [1.] Clowse M. Arthritis Rheumatol 2024;76 (suppl 9). **Acknowledgements:** This study was funded by UCB and Biogen. Medical writing support provided by Costello Medical and funded by UCB and Biogen.

O010 / #827

Topic: *AS07 - Cutaneous Lupus*
Late-Breaking Abstract

ABSTRACT CONCURRENT SESSION 01: FINDINGS FROM LUPUS CLINICAL TRIALS
22-05-2025 1:40 PM - 2:40 PM

RANDOMIZED, PLACEBO-CONTROLLED PHASE II STUDY OF ENPATORAN, A SMALL MOLECULE TOLL-LIKE RECEPTOR 7/8 INHIBITOR, IN CUTANEOUS LUPUS ERYTHEMATOSUS: RESULTS FROM COHORT A

David Pearson[1], Eric Morand[2], Joerg Wenzel[3], Richard Furie[4], Maria Dall'Era[5], Jorge Sanchez-Guerrero[6], Sanjeev Roy[7], Summer Goodson[8], Hans Gühring[9], Flavie Moreau[10], Victoria P. Werth[11]
[1]Department of Dermatology, University of Minnesota, Minneapolis, United States of America, [2]Centre for Inflammatory Diseases, Monash University, Melbourne, Australia, [3]Department of Dermatology and Allergy, University Hospital of Bonn, Bonn, Germany, [4]Division of Rheumatology, Northwell Health, Great Neck, United States of America, [5]Division of Rheumatology, University of California San Francisco School of Medicine, San Francisco, United States of America, [6]Division of Rheumatology, Mount Sinai Hospital/Toronto Western Hospital, University of Toronto, Toronto, Canada, [7]Global Clinical Development, Ares Trading SA, an affiliate of Merck KGaA, Darmstadt, Germany, Eysins, Switzerland, [8]EMD Serono, Inc., Rockland, United States of America, [9]The healthcare business of Merck KGaA, Darmstadt, Germany, [10]EMD Serono, Billerica, United States of America, [11]Department of Dermatology, Perelman School of Medicine, University of Pennsylvania and Philadelphia VAMC, Philadelphia, United States of America

Background/Purpose: No treatment is approved for cutaneous lupus erythematosus (CLE), which may occur in the presence or absence of systemic lupus erythematosus (SLE). Enpatoran is an oral small molecule toll-like receptor 7/8 inhibitor, with potential to modulate processes central to CLE and SLE pathophysiology. WILLOW (NCT05162586) is a Phase II randomized double-blind placebo-controlled dose-finding parallel adaptive study in adults with SLE or CLE receiving standard of care to evaluate the efficacy and safety of enpatoran. WILLOW Cohort A enrolled patients with CLE or SLE who had active lupus rash.

Methods: Patients with Cutaneous Lupus Disease Area and Severity Index-Activity (CLASI-A) score ≥ 8 CLE were enrolled; they had CLE only, or SLE with mild or no extra-mucocutaneous disease activity [British Isles Lupus Assessment Group 2004 < 1B, C, D]). Patients were randomized 1:1:1:1 to one of three doses of enpatoran or placebo for 24 weeks, with an additional 2-week safety follow-up for patients not choosing to enter the long-term extension. The primary objective was to evaluate the dose-response

relationship of enpatoran in reducing disease activity, based on change from baseline in CLASI-A score at Week 16. Secondary endpoints included change from baseline in Physician's Global Assessment at Weeks 16 and 24, clinically meaningful corticosteroid (CS) reduction, and occurrence of Cutaneous Lupus Activity-Investigator Global Assessment 0 or 1 at Week 16 and Week 24. Exploratory endpoints included CLASI-A improvement ≥ 50%/70% (CLASI-50/70). Treatment-emergent adverse events (TEAEs), serious TEAEs, TEAEs of special interest and laboratory parameters were collected from Day 1 to the end of safety follow-up.

Results: 102 patients were randomized, and 100 patients were included for efficacy evaluation (placebo n = 26; enpatoran low dose n = 23; mid dose n = 25; high dose n = 26). 77.0% of patients were female, and 58.0% had CLE only. At baseline, 59.0% of patients were receiving systemic CS, 38.0% immunosuppressants and 76.0% antimalarials; 71% had moderate-to-severe disease (CLASI-A ≥ 10). The primary outcome was achieved. At Week 16, a significant dose response for enpatoran in reducing CLASI-A from baseline was detected (p = 0.0002) (Table 1).

Table 1 Dose-response relationship of enpatoran in reducing disease activity based on change from baseline in CLASI-A score at Week 16 (FAS; N = 100)

	Placebo	Enpatoran dose		
	(n = 26)	Low (n = 23)	Mid (n = 25)	High (n = 26)
Primary analysis: Based on MCP-Mod				
Detection of a dose-response relationship			P = 0.0002	
Selected model			Log-linear (E0 = −44.3, Delta = −6.0)	
Adjusted means in change from baseline in CLASI-A score at Week 16, % (95% CI)	−44.3 (−55.1, −33.4)	−63.9 (−70.0, −57.7)	−67.9 (−74.8, −61.1)	−72.0 (−80.1, −64.0)

MCP-Mod adjusted for CLASI-A at baseline, region and disease diagnosis (CLE only vs CLE + SLE).
CI, confidence interval; CLASI-A, Cutaneous Lupus Disease Area and Severity Index-Activity; FAS, full analysis set; MCP-Mod, multiple comparison procedures-modelling.

Furthermore, up to 91.3% of patients receiving enpatoran achieved CLASI-50, and up to 60.9% achieved CLASI-70 at Week 16, compared with 38.5% and 11.5% of patients, respectively, receiving placebo. Enpatoran was well tolerated across all study doses. High-dose enpatoran was associated with a higher rate of TEAEs (Table 2) than lower doses or placebo; the most frequently reported TEAEs were infections and infestations.

Table 2 Treatment-emergent adverse events (SAS; N = 102)

	Placebo (n = 26)	Enpatoran dose		
		Low (n = 24)	Mid (n = 26)	High (n = 26)
Any TEAE, n (%)	12 (46.2)	15 (62.5)	15 (57.7)	21 (80.8)
Any treatment-related TEAE, n (%)	2 (7.7)	8 (33.3)	8 (30.8)	7 (26.9)
Any serious TEAE, n (%)	1 (3.8)	2 (8.3)	0 (0)	1 (3.8)
Any TEAE of special interest[a], n (%)	0 (0)	0 (0)	0 (0)	2 (7.7)[b]

[a]TEAEs considered to be of special interest were: severe infections (Grade ≥ 3); seizure (any Grade); clinically significant cardiac arrhythmia; serotonin syndrome; [b]Bradyarrhythmia (n = 1); herpes zoster (n = 1).
SAS, safety analysis set; TEAE, treatment emergent adverse event.

Conclusions: Enpatoran demonstrated a significant dose response in change from baseline in CLASI-A compared with placebo at Week 16 in patients with CLE or SLE and was well tolerated. **Acknowledgments:** The authors wish to thank Dominika Weinelt for their support with the study conduct and analysis. Medical writing support was provided by Nicole Jones on behalf of Amica Scientific, Macclesfield, UK, and sponsored by the healthcare business of Merck KGaA, Darmstadt, Germany.

O011 / #377

Topic: ***AS19 - Patient-Reported Outcome Measures***

ABSTRACT CONCURRENT SESSION 01: FINDINGS FROM LUPUS CLINICAL TRIALS
22-05-2025 1:40 PM - 2:40 PM

DAPIROLIZUMAB PEGOL DEMONSTRATED IMPROVEMENT IN QUALITY OF LIFE OF PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS: LUPUSQOL RESULTS FROM A PHASE 3 TRIAL

Zahi Touma[1], Cynthia Aranow[2], Ioannis Parodis[3,4], Rosalind Ramsey-Goldman[5], Matthias Schneider[6], Christine De La Loge[7], Teri Jimenez[8], Mina Nejati[9], Laurent Arnaud[10]
[1]University of Toronto Lupus Clinic, Division of Rheumatology, Schroeder Arthritis Institute, Krembil Research Institute, University Health Network, Toronto, Canada, [2]Institute of Molecular Medicine, Feinstein Institutes for Medical Research, Manhasset, United States of America, [3]Division of Rheumatology, Department of Medicine Solna, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden, [4]Department of Rheumatology, Faculty of Medicine and Health, Örebro University, Örebro, Sweden, [5]Feinberg School of Medicine, Northwestern University, Chicago, United States of America, [6]Clinic of Rheumatology and Hiller Research Unit, Heinrich-Heine-University, Düsseldorf, Germany, [7]UCB, Brussels, Belgium, [8]UCB, Raleigh, United States of America, [9]Biogen, Cambridge, United States of America, [10]Department of Rheumatology, National Reference Center for Autoimmune Diseases (RESO), University Hospitals Strasbourg, Strasbourg, France

Background/Purpose: Systemic lupus erythematosus (SLE) imposes significant disease burden and diminishes health-related quality of life (HRQoL); improvement of HRQoL is therefore a key treatment goal in SLE.[1,2] Dapirolizumab pegol (DZP) is a novel, polyethylene glycol (PEG)-conjugated antigen-binding (Fab') fragment, lacking an Fc domain, that inhibits CD40L signaling. In the phase 3 PHOENYCS GO trial (NCT04294667) in patients with SLE, DZP improved disease activity measured by clinician-reported outcomes at Week 48 vs placebo (PBO), and was generally well tolerated.[3] Here, we report the impact of DZP on HRQoL as measured by LupusQoL completed by patients in the PHOENYCS GO trial.

Methods: PHOENYCS GO was a 48-week, randomized, double-blind, PBO-controlled trial. Patients aged ≥ 16 years with moderate-to-severe, active SLE characterized by persistently active or frequently flaring/relapsing-remitting disease activity despite stable standard of care (SOC) medication (antimalarials, corticosteroids, and/or immunosuppressants) were included. Patients were randomized 2:1 to intravenous DZP 24 mg/kg plus SOC medication (DZP+SOC) or PBO+SOC every 4 weeks. HRQoL outcomes were measured using LupusQoL, a patient-reported outcome based on responses on a 5-point Likert scale to 34 items across eight HRQoL domains.[1] Each

domain score ranges from 0 to 100; higher scores indicate better HRQoL. The least square (LS) mean change from baseline in LupusQoL domain scores at Weeks 12, 24, 36, and 48 are reported. The LS mean, difference for DZP+SOC vs PBO+SOC, and 95% CIs were computed using a mixed model for repeated measurements (MMRM). Analyses were performed on the full analysis set.

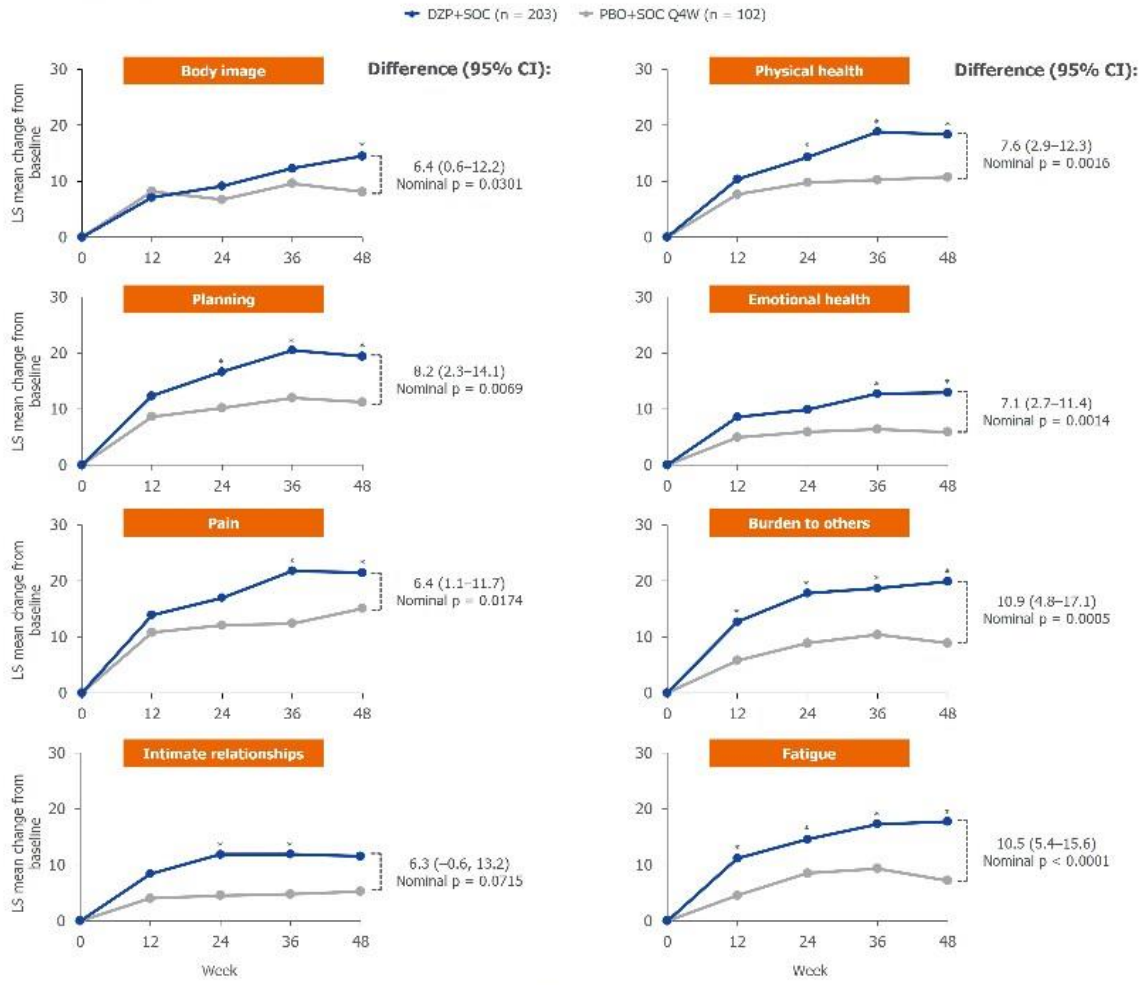
Results: Overall, 97.6% (203/208) of patients receiving DZP+SOC and 95.3% (102/107) of patients receiving PBO+SOC had LupusQoL responses available at any visit. Baseline LupusQoL scores were comparable between the treatment groups (**Table**). Patients receiving DZP+SOC demonstrated consistently greater improvements from baseline over time in LupusQoL scores across all domains compared with PBO+SOC (**Figure**). Patients receiving DZP+SOC reported greater improvements in the 'Fatigue' and 'Burden to others' domains at all assessed visits compared with those receiving PBO+SOC, as of Week 12 (all $p < 0.05$; nominal). Additionally, greater improvements were reported for patients receiving DZP+SOC compared with PBO+SOC in the 'Physical health' and 'Planning' domains at Weeks 24, 36, and 48, in the 'Pain' and 'Emotional health' domains at Weeks 36 and 48, in the 'Intimate relationships' domain at Weeks 24 and 36, and in the 'Body image' domain at Week 48 (each $p < 0.05$; nominal).

Table. Baseline LupusQoL domain scores

	DZP+SOC n = 203	PBO+SOC n = 102
LupusQoL domain scores, mean (SD)		
Body image	63.0 (24.0)[a]	64.3 (27.3)[b]
Physical health	54.2 (23.6)	55.8 (22.3)
Planning	58.1 (29.5)	58.1 (29.3)
Emotional health	66.1 (21.7)[c]	69.0 (19.9)
Pain	52.8 (26.1)	53.7 (25.9)
Burden to others	52.1 (28.3)	54.0 (27.7)
Intimate relationships	58.3 (32.4)[d]	60.0 (32.6)[e]
Fatigue	52.4 (25.6)	52.6 (24.5)

Full analysis set. [a]n = 184; [b]n = 94; [c]n = 202; [d]n = 174; [e]n = 91. DZP: dapirolizumab pegol; LupusQoL: Lupus Quality of Life; PBO: placebo; SD: standard deviation; SOC: standard of care.

Figure. LS mean change from baseline in LupusQoL domain scores by visit (MMRM)



Full analysis set. *Nominal p < 0.05 for the DZP+SOC vs PBO+SOC comparison. Higher LupusQoL scores correspond with better HRQoL. The LS mean, difference for DZP+SOC vs PBO+SOC, and 95% CIs were computed using MMRM. CI: confidence interval; DZP: dapirolizumab pegol; HRQoL: health-related quality of life; LS: least square; LupusQoL: Lupus Quality of Life; MMRM: mixed model for repeated measurements; PBO: placebo; SOC: standard of care.

Conclusions: Improvements in HRQoL were greater in patients treated with DZP+SOC vs PBO+SOC across all LupusQoL domains, starting at the earliest time point (Week 12)

for some domains. These data, along with the previously reported significant improvements in overall disease activity,[3] support the potential of DZP as a valuable treatment option in SLE to improve HRQoL. **References:** [1.] McElhone K. Arthritis Care Res 2007;57:972–9. [2.] Fanouriakis A. Ann Rheum Dis 2019;78:736–45. [3.] Clowse M. Arthritis Rheumatol 2024;76 (suppl 9). **Acknowledgements:** This study was funded by UCB and Biogen. Medical writing support provided by Costello Medical and funded by UCB and Biogen.

O012 / #232

Topic: ***AS15 - Lupus Nephritis-Clinical***

ABSTRACT CONCURRENT SESSION 01: FINDINGS FROM LUPUS CLINICAL TRIALS
22-05-2025 1:40 PM - 2:40 PM

ACHIEVEMENT OF PROTEINURIA LESS THAN 0.4 G/G IN THE PHASE 3 AURORA 1 STUDY OF VOCLOSPORIN IN LUPUS NEPHRITIS

Maria Dall'Era[1], Brad Rovin[2], Salem Almaani[2], Lily Cipolla[3], Vanessa Birardi[3], Ernie Yap[3]
[1]University of California San Francisco, Department Of Rheumatology, San Francisco, United States of America, [2]The Ohio State University Wexner Medical Center, Columbus, United States of America, [3]Aurinia Pharmaceuticals Inc., Edmonton, Canada

Background/Purpose: Reduction in urine protein creatine ratio (UPCR) is the cornerstone of the definition of treatment response in lupus nephritis. Treatment guidelines have incorporated various UPCR targets as goals of therapy, with UPCR <0.5 g/g being at the lower end.[1,2] However, studies demonstrate that low-grade proteinuria, even <0.5 g/g, is often associated with significant histologic activity.[3] Therefore, targeting lower UPCR levels may be beneficial to patients. Using data from the 52-week, Phase 3 AURORA 1 study in lupus nephritis, this post-hoc analysis assessed achievement of UPCR targets <0.4 g/g with a voclosporin-based therapy.

Methods: Key inclusion criteria for the AURORA 1 study included biopsy-proven active LN, UPCR ≥1.5 g/g (≥2 g/g for Class V) and estimated glomerular filtration rate (eGFR) >45 mL/min/1.73 m^2). Participants were randomized to either voclosporin (23.7 mg) or matching placebo (control) twice daily, in combination with MMF (target 2 g/day) and low-dose glucocorticoids (starting dose 20-25 mg/day, tapered to ≤2.5 mg/day by Week 16). Achievement at any study visit of UPCR targets <0.4 g/g, <0.3 g/g, <0.2 g/g, and <0.1 g/g was assessed. Baseline demographics, disease characteristics and safety outcomes are described for the subgroup of participants with UPCR <0.4 g/g at any study visit.

Results: Of the 357 participants in AURORA 1, 109 (60.9%) voclosporin-treated participants and 66 (37.1%) control-treated participants achieved a UPCR <0.4 g/g at least once during the 52-week study (Table 1). Of these 175 participants with UPCR <0.4 g/g, 87% were female, and mean (SD) age was 34 (11.2) years. A total of 13% had Class III lupus nephritis, 49% had Class IV, 16% had Class V, and 40% had mixed disease. The median (range) time since diagnosis of lupus nephritis was 1.1 (0-27.0) years. The overall incidence of adverse events was similar between the two treatment groups (voclosporin, 89.9%; control, 83.3%). Mean eGFR remained stable and within the normal range in both groups (Figure 1).

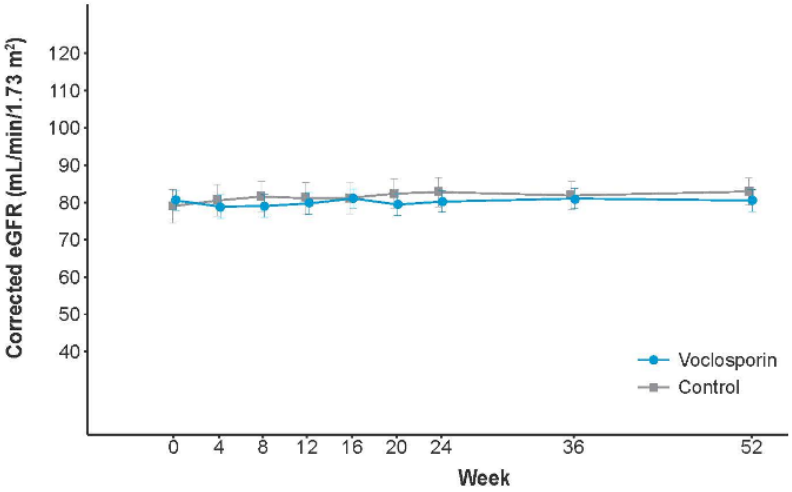
Conclusions: Nearly half of the AURORA 1 population achieved a UPCR <0.4 g/g at least once during the 52-week study. Participants treated with voclosporin achieved lower UPCR targets at substantially higher rates than control-treated participants, with comparable rates of adverse events. These data provide initial evidence that targeting lower UPCR targets is feasible and enhanced with the use of voclosporin-based therapy. **References** 1. Rovin BH, Ayoub IM, Chan TM, et al. Executive summary of the KDIGO 2024 Clinical Practice Guideline for the Management of Lupus Nephritis. *Kidney Int*. 2024;105(1):31-34. doi:10.1016/j.kint.2023.09.001 2. Fanouriakis A, Kostopoulou M, Andersen J, et al. EULAR recommendations for the management of systemic lupus erythematosus: 2023 update. *Ann Rheum Dis*. Jan 2 2024;83(1):15-29. doi:10.1136/ard-2023-224762 3. De Rosa M, Rocha AS, De Rosa G, Dubinsky D, Almaani SJ, Rovin BH. Low-Grade Proteinuria Does Not Exclude Significant Kidney Injury in Lupus Nephritis. *Kidney Int Rep*. Jul 2020;5(7):1066-1068. doi:10.1016/j.ekir.2020.04.005

Table 1. Proteinuria Reductions Achieved in AURORA 1

UPCR, n (%)	Control n=178	Voclosporin n=179	Overall N=357
<0.4 g/g	66 (37.1)	109 (60.9)	175 (49.0)
<0.3 g/g	56 (31.5)	96 (53.6)	152 (42.6)
<0.2 g/g	42 (23.6)	72 (40.2)	114 (31.9)
<0.1 g/g	16 (9.0)	37 (20.7)	53 (14.8)

Analysis includes all 357 participants of the AURORA 1 study. UPCR targets are not mutually exclusive; participants may have achieved more than one UPCR cut-off at any study visit.

Figure 1. Mean Corrected eGFR in Participants Achieving UPCR <0.4 g/g



Voclosporin (n)	109	109	105	105	105	104	103	99	93
Control (n)	66	66	65	64	63	62	63	62	61

Data are from 175 patients in the AURORA 1 study who achieved UPCR <0.4 g/g at any study visit. Baseline least square means and 95% CI are calculated from a model including a covariate for treatment group. Post-baseline least square means and 95% CI are calculated from a model including covariates for treatment group and baseline value. Renal function assessed with corrected eGFR (Chronic Kidney Disease Epidemiology Collaboration equation) using a prespecified ceiling of 90 mL/min/1.73 m^2. Estimated glomerular filtration rate, eGFR.

O013 / #551

Topic: ***AS23 - SLE-Diagnosis, Manifestations, & Outcomes***

ABSTRACT CONCURRENT SESSION 02: SLE METRICS – IMPROVING OUTCOMES & MEASURES
22-05-2025 1:40 PM - 2:40 PM

DEVELOPING AND EVALUATING A LABORATORY-BASED FRAILTY INDEX (FI-LAB) FOR THE PREDICTION OF LONG-TERM HEALTH OUTCOMES IN SYSTEMIC LUPUS ERYTHEMATOSUS

Grace Burns, Alexandra Legge
Dalhousie University, Medicine, Halifax, Canada

Background/Purpose: Frailty is a useful measure of health status in systemic lupus erythematosus (SLE), but it is not routinely captured in existing SLE datasets. In other populations, frailty indices constructed exclusively from laboratory data have been shown to predict adverse health outcomes. We aimed to construct and evaluate the first laboratory-based frailty index (FI-Lab) for people living with SLE. Additionally, we compared the FI-Lab to an existing clinical frailty index with respect to the prediction of future health outcomes.

Methods: This study used existing data from a single-center prospective cohort of adult SLE patients followed annually with standardized clinical and laboratory assessments. We included the first study visit for each patient occurring between 2010 and 2019, with follow-up data available until June 2024. All participants met the 1997 revised American College of Rheumatology (ACR) classification criteria for SLE. A 30-item FI-Lab was constructed by adapting the list of laboratory variables previously identified by Ellis et al. [1]. Baseline FI-Lab scores were calculated for each patient. Using clinical data, a baseline Systemic Lupus International Collaborating Clinics Frailty Index (SLICC-FI) score was calculated for each patient. Organ damage accrual was defined as the change in SLICC/ACR Damage Index (SDI) score from the baseline visit to the last follow-up visit. Mortality was defined as any recorded death within the follow-up period. Cox proportional hazards regression was used to examine the association between baseline FI-Lab scores and all-cause mortality risk, while negative binomial regression was used to evaluate the association of baseline FI-Lab scores with organ damage accrual during follow-up. To compare the performance of models containing the baseline FI-Lab and/or SLICC-FI as predictor variables, we used Akaike information criterion (AIC), Harrell's C-statistic, and pseudo-R^2 values.

Results: The 283 included patients (89% female) had a mean (SD) age of 47.7 (15.1) years and a median (IQR) disease duration of 8.3 (2.6-19.8) years at baseline. The 97 patients (34.3%) classified as frail at baseline (based on FI-Lab scores > 0.21) had

increased mortality risk [hazard ratio 3.71; 95% CI 1.82-7.54] compared to non-frail patients **(Figure 1)**. Baseline frailty was also associated with a higher rate of organ damage accrual during follow-up [incidence rate ratio 2.26; 95% CI 1.59-3.22]. A weak correlation existed between baseline FI-Lab and SLICC-FI scores (r_s=0.37, p<0.001). In unadjusted analysis, higher baseline FI-Lab and SLICC-FI scores were both associated with increased mortality risk during follow-up. However, after multivariable adjustment, only the FI-Lab maintained a significant association with mortality risk **(Table 1)**. Both the FI-Lab and the SLICC-FI were significant baseline predictors of organ damage accrual during follow-up, and the multivariable model that included both frailty measures was superior to the models containing either the FI-Lab or the SLICC-FI alone **(Table 1)**.

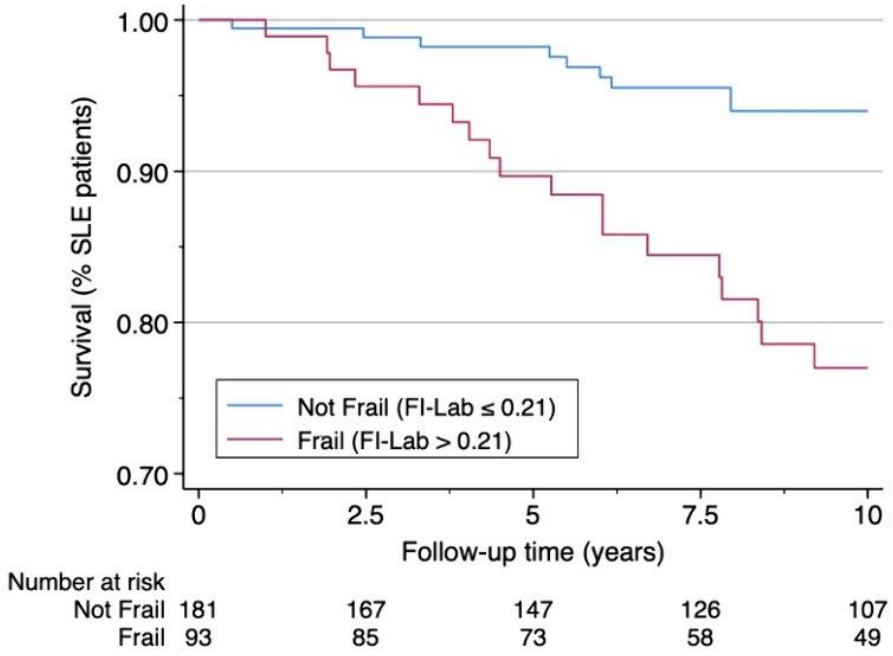


Figure 1. Kaplan-Meier survival curves for mortality risk during follow-up among SLE patients who were classified as frail at baseline (in red) versus non-frail SLE patients (in blue) based on laboratory-based frailty index (FI-Lab) scores.

Table 1. Association of baseline FI-Lab and SLICC-FI scores with mortality risk and organ damage accrual during follow-up (n=274).

	All-cause Mortality Risk [a]				Organ Damage Accrual [b,c]			
	HR (95% CI)	**p-value**	**AIC**	**C-statistic**	**IRR (95% CI)**	**p-value**	**AIC**	**Pseudo R^2**
Multivariable model 1: FI-Lab			305.07	0.8473			589.95	0.1097
FI-Lab (per 0.05 increase)	1.28 (1.09, 1.51)	p= 0.003			1.14 (1.06, 1.23)	p= 0.001		
Multivariable model 2: SLICC-FI			310.65	0.8380			587.36	0.1138
SLICC-FI (per 0.05 increase)	1.24 (0.95, 1.63)	p= 0.109			1.24 (1.11, 1.39)	p < 0.0001		
Multivariable model 3: FI-Lab + SLICC-FI			306.96	0.8470			584.26	0.1219
FI-Lab (per 0.05 increase)	1.26 (1.05, 1.52)	p= 0.015			1.10 (1.01, 1.18)	p= 0.021		
SLICC-FI (per 0.05 increase)	1.05 (0.78, 1.43)	p= 0.732			1.18 (1.05, 1.33)	p= 0.005		

[a]Multivariable models adjusted for the following baseline characteristics: Age (in years), sex, SLE disease duration (in years), education level, cigarette smoking status, baseline SLICC/ACR damage index (SDI) score, antimalarial use, and anticoagulant use.
[b]Multivariable models adjusted for the following baseline characteristics: Age (in years), sex, race, SLE disease duration (in years), education level, cigarette smoking status, baseline SDI score, immunosuppressant use, and anticoagulant use.
[c]Rate of organ damage accrual per person-year of follow-up based on the change in SDI score from the baseline visit to the last study visit during follow-up.
HR= hazard ratio; CI= confidence interval; AIC= Akaike information criterion; IRR= incidence rate ratio; FI-Lab = laboratory-based frailty index; SLICC-FI = Systemic Lupus International Collaborating Clinics Frailty Index.

Conclusions: An FI constructed from routinely collected laboratory variables can measure frailty and predict future health outcomes in SLE. The FI-Lab may serve as a convenient screening tool to detect subclinical deficit accumulation and promote early risk mitigation among SLE patients. References: [1.] Ellis HL. CMAJ 2020;192(1):E3-E8.

O014 / #382

Topic: ***AS23 - SLE-Diagnosis, Manifestations, & Outcomes***

ABSTRACT CONCURRENT SESSION 02: SLE METRICS – IMPROVING OUTCOMES & MEASURES
22-05-2025 1:40 PM - 2:40 PM

DELAYED DIAGNOSIS IN SYSTEMIC LUPUS ERYTHEMATOSUS

Romina Nieto[1], Lucia Hernandez[2], Nidia Noemí Merás[3], Florencia Bordón[4], Cintia Otaduy[5], Lucila García[6], Rosa Serrano Morales[1], Nicolás Pérez[7], Micaela Cosatti[8], Ana Carolina De Oliveira E Silva Montandon[9], Gustavo Flores Chapacais[10], Laissa Cristina Alves Alvino[11], Emily F. N. Yuki[12], Eloisa Bonfá[12], Alexis Bondi Peralta[13], Loreto Massardo[14], Andrés Angelo Cadena Bonfanti[15], Andrés Hormaza[16], José Maximiliano Martínez Pérez[17], Olga Lidia Vera Lastra[18], Hilda Fragoso Loyo[19], Yaneli Juárez-Vicuña[20], Diana Fernandez[21], Patricia Elena Langjahr[22], María Teresa Martínez De Filartiga[23], Manuel Francisco Ugarte-Gil[24], Carlos Alejandro Loayza Flores[25], Teresandris Polanco Mora[26], María Belén Lecumberri[27], Álvaro Danza[28], Carlos Enrique Toro Gutiérrez[29], Urbano Sbarigia[30], Ashley Orillion[31], Federico Zazzetti[32], Graciela S. Alarcón[33,34], Bernardo A. Pons-Estel[1], Guillermo Pons-Estel[1]
[1]Centro Regional de Enfermedades Autoinmunes y Reumáticas, Grupo Oroño, Rosario, Argentina, [2]Consultora externa de GLADEL, Rosario, Argentina, [3]Hospital Italiano de Córdoba, Córdoba, Argentina, [4]Hospital Privado Universitario de Córdoba, Córdoba, Argentina, [5]Sección de Reumatología, Hospital Córdoba, Córdoba, Argentina, [6]Servicio de Reumatología del HIGA San Martín, La Plata, Argentina, [7]Instituto de Investigaciones Médicos Alfredo Lanari, Universidad de Buenos Aires, Buenos Aires, Argentina, [8]CEMIC Centro de Educación Médica e Investigaciones Clínicas "Norberto Quirno", CABA, Argentina, [9]Unidade de Especialidades Clínicas - Hospital das Clínicas UFG / Ebserh Goiânia, Goias, Brazil, [10]Rheumatology División, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil, [11]Hospital Universitario Pedro Ernesto, Rio de Janeiro, Brazil, [12]Rheumatology División, Hospital das Clínicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil, [13]Hospital del Salvador, Santiago de Chile, Chile, [14]Centro de Biologia Celular y Biomedicina CEBICEM. Universidad San Sebastián, SANTIAGO, Chile, [15]Clínica de La Costa - Universidad Simón Bolívar Barranquilla, Barranquilla, Colombia, [16]Fundación Valle del Lili, Unidad de Reumatología, Cali, Colombia, [17]Hospital de Especialidades Alfredo Paulson, Guayaquil, Ecuador, [18]Departamento de Reumatología, Hospital de Especialidades Dr. Antonio Fraga Mouret, CMN La Raza IMSS, Mexico, Mexico, [19]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, mexico, Mexico, [20]Instituto Nacional de Cardiología Ignacio Chávez, Departamento de Inmunología, Mexico, Mexico, [21]Member of GLADEL, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [22]Facultad de Ciencias Químicas, Universidad Nacional de

Asunción, Asunción, Paraguay, [23]Cátedra de Inmunología Facultad de Ciencias Medicas. Universidad Nacional de Asunción, Asunción, Paraguay, [24]Grupo Peruano de Estudio de Enfermedades Autoinmunes Sistemicas. Universidad Cientifica del Sur. Lima, Peru. Servicio de Reumatología. Hospital Guillermo Almenara Irigoyen, EsSalud, Lima, Peru, [25]Hospital Cayetano Heredia. Universidad Peruana Cayetano Heredia, Lima, Peru, [26]Reumatología-Hospital Docente Padre Billini - Santo Domingo, Santo Domingo, Dominican Republic, [27]Hospital Señor del Milagro, Salta, Argentina, [28]Médica Uruguaya Corporación de Asistencia Médica (MUCAM). Clínica Médica - Facultad de Medicina - UdelaR, Montevideo, Uruguay, [29]Centro de Referencia en Osteoporosis & Reumatología, Cali, Colombia, [30]Janssen Pharmaceutica NV, Brussels, Belgium, [31]Janssen Research & Development, LLC, a Johnson & Johnson Company, Spring House, United States of America, [32]Janssen Global Services, LLC, a Johnson & Johnson Company, Horsham, United States of America, [33]División of Clinical Immunology and Rheumatology, The University of Alabama at Birmingham Marnix Heersink School of Medicine, Birmingham, United States of America, [34]Department of Medicine, School of Medicine, Universidad Peruana Cayetano, Heredia, Lima, Peru

Background/Purpose: Systemic lupus erythematosus (SLE) is a multi-systemic autoimmune disease of unknown etiology. Diagnosis is often delayed because it frequently mimics symptoms of other diseases; this also delays treatment initiation. Previous studies have reported that this delay in diagnosis was associated with a worse prognosis including higher disease activity, damage accrual, decreased quality of life and increased use of healthcare resources and, therefore, higher costs. In the Grupo Latino Americano de Estudio del Lupus (GLADEL) original cohort, a maximum time to SLE diagnosis of 24 months did not negatively influence disease outcomes (damage accrual and mortality)[1]. This study aimed to characterize delay in the diagnosis in SLE patients and its associated factors.

Methods: GLADEL 2.0 is an observational multi-ethnic, multi-national Latin-American SLE cohort. Forty-three centers from 10 Latin-American countries enrolled patients ≥ 18 years of age who fulfilled the 1982/1997 American College of Rheumatology (ACR) and/or the 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria. Patients were categorized into 4 subsets according to the presence or absence of active or inactive lupus nephritis (LN)[2]. Baseline demographics, clinical manifestations, disease activity (SLEDAI-2K), SLICC/ACR damage index (SDI), and treatments were examined. Based on the original GLADEL report, variables were examined according to time to diagnosis shorter versus equal or longer than 24 months, as no impact was found on outcomes before this time[1]. Continuous variables are summarized as median (Q1, Q3) and categorical variables as counts and percentages. Logistic regression models were used to identify factors independently associated with a delay in diagnosis ≥ 24 months. P-values < 0.05 were considered significant. All analyses were done using R v4.4.0.

Results: Of the 1083 patients included in this GLADEL cohort, 985 were included in these analyses. The remaining patients were excluded because of insufficient data for analysis. The median time to diagnosis was 8 months (0.27–5.67); in 97 patients (9.84%) the time to diagnosis was ≥ 24 months. Table 1 depicts the sociodemographic and clinical characteristics of SLE patients according to time to diagnosis. Patients with a time to diagnosis ≥ 24 months were found to be older at diagnosis, having a higher frequency of thrombocytopenia, associated comorbidities, antiphospholipid syndrome (APS), anti-beta-2-glycoprotein I (B2GPI) positivity and cumulative damage with lower frequency of low complement at cohort entry. After adjusting for sociodemographic, clinical and immunologic features, multivariate analysis showed that older age, middle socioeconomic status and associated APS were associated with a higher probability of diagnostic delay (Table 2).

Table 1. Clinical and sociodemographic characteristics of SLE patients from the GLADEL 2.0 cohort according to time to diagnosis

Variable	< 24 months (n = 888)	≥ 24 months (n = 97)	*p*-value
Time at diagnosis (months), median (Q1, Q3)	0.6 (0.1-3.3)	48.2 (31.5-72)	0.000
Age at diagnosis (years), median (Q1, Q3)	26 (20-34)	30 (23-41)	0.001
Female Gender, n (%)	790 (89.0%)	87 (89.7%)	1.000
Ethnicity, n (%)			0.822
Caucasian	226 (25.5%)	23 (23.7%)	
African Latin American	68 (7.7%)	9 (9.3%)	
Mestizo[†]	583 (65.9%)	64 (66.0%)	
Other	8 (0.9%)	1 (1.0%)	
Socioeconomic status, n (%)			0.029
High	188 (21.5%)	32 (34.0%)	
Medium	318 (36.3%)	29 (30.9%)	
Medium low/Low	369 (42.2%)	33 (35.1%)	
Medical insurance, n (%)	608 (69.2%)	68 (70.8%)	0.816
Cumulative clinical manifestations, n (%)			
Fever	370 (41.7%)	40 (41.2%)	1.000
Malar rash	556 (62.6%)	53 (54.6%)	0.152
Discoid lupus	69 (7.8%)	11 (11.3%)	0.239
Photosensitivity	564 (63.9%)	57 (58.8%)	0.319
Oral/nasopharyngeal ulcers	386 (43.9%)	44 (45.4%)	0.830
Alopecia	576 (65%)	69 (71.1%)	0.261
Arthritis	722 (81.3%)	80 (82.5%)	0.891
Pleuritis	228 (25.8%)	25 (25.8%)	1.000
Pericarditis	161 (18.3%)	13 (13.4%)	0.265
Persistent proteinuria	508 (57.4%)	49 (50.5%)	0.197
Cellular cylinders	229 (27.2%)	27 (28.4%)	0.809
Psychosis	29 (3.3%)	2 (2.1%)	0.761
Seizures	42 (4.7%)	8 (8.2%)	0.143
Hemolytic anemia	101 (11.5%)	15 (15.6%)	0.244
Leukopenia	401 (45.9%)	45 (47.4%)	0.829
Lymphopenia	478 (54.6%)	51 (53.7%)	0.914
Thrombocytopenia	193 (22.1%)	33 (34.4%)	0.010
Positive ANA	872 (99.3%)	94 (97.9%)	0.182
Anti-dsDNA, positivity	676 (78.4%)	73 (77.7%)	0.895
Anti-Sm, positivity	269 (36.4%)	25 (29.4%)	0.232
Anti-lupus coagulant, positivity	114 (16.2%)	18 (21.7%)	0.214
Anti-cardiolipin, positivity	141 (19.0%)	23 (27.1%)	0.085
Anti-B2GPI, positivity	67 (11.2%)	19 (26.8%)	0.001
False-positive VDRL	26 (4.1%)	7 (9.7%)	0.068
C3, low	681 (78.5%)	66 (68.8%)	0.038
C4, low	682 (78.9%)	66 (68.8%)	0.027
CH50, low	68 (27.5%)	4 (15.4%)	0.243
Coombs positive	146 (23.9%)	23 (33.8%)	0.077
Comorbidities[‡], n (%)	428 (48.4%)	60 (61.9%)	0.014
SLEDAI at cohort entry, median (Q1, Q3)	5 (2-12)	6 (2-12)	0.634
SDI at cohort entry ≥ 1, n (%)	316 (36.6%)	48 (51.1%)	0.007
Personal history of autoimmune diseases, n (%)			
Sjogren's Syndrome	29 (3.3%)	5 (5.2%)	0.371
RA	8 (0.9%)	1 (1.0%)	0.608
APS	51 (5.8%)	13 (13.5%)	0.008

[‡]At least one of the following: diabetes mellitus, arterial hypertension, dyslipidemia. [†]Mestizo: individuals born in Latin America who had both Amerindian and white ancestors. anti-dsDNA: anti-double stranded deoxyribonucleic acid; ANA, antinuclear antibody; anti-Sm, anti-Smith; B2GPI, Beta-2-glycoprotein I; APS, antiphospholipid syndrome; RA, rheumatoid arthritis SDI, SLICC/ACR damage index; SLE, Systemic Lupus Erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SLICC, Systemic Lupus International Collaborating Clinics; VDRL, Venereal Disease Research Laboratory.

Table 2. Univariable and multivariable Cox regression analyses of factors associated with delayed diagnosis in SLE patients from the GLADEL 2.0 cohort

Variable	Univariate Model Odds Ratio (OR) (95% CI)	*p*-value	Multivariate Model Odds Ratio (OR) (95% CI)	*p*-value
Gender, Female	1.08 (0.54, 2.15)	0.828	1.24 (0.56, 2.78)	0.595
Age at diagnosis	1.03 (1.02, 1.05)	< 0.001	1.03 (1.01, 1.05)	0.004
Ethnicity				
Caucasian	Ref		Ref	
African Latin American	1.30 (0.57, 2.94)	0.528	1.28 (0.49, 3.31)	0.616
Mestizo†	1.08 (0.65, 1.78)	0.767	1.08 (0.62, 1.89)	0.792
Other	1.23 (0.15, 10.26)	0.849	1.35 (0.15, 12.14)	0.791
Socioeconomic status				
High	Ref		Ref	
Medium	0.54 (0.31, 0.91)	0.022	0.48 (0.25, 0.89)	0.021
Medium low / low	0.53 (0.31, 0.88)	0.015	0.55 (0.29, 1.06)	0.072
Educational level, years				
0-7	Ref		Ref	
8 to 12	1.57 (0.60, 4.12)	0.359	1.68 (0.60, 4.65)	0.321
13 or more	1.47 (0.57, 3.83)	0.427	1.4 (0.48, 4.05)	0.537
SDI at cohort entry ≥ 1	1.81 (1.18, 2.77)	0.007	1.24 (0.74, 2.08)	0.412
SLEDAI at cohort entry	1.01 (0.98, 1.03)	0.604	1.02 (0.99, 1.06)	0.161
Comorbidities*	1.73 (1.13, 2.66)	0.012	1.31 (0.79, 2.16)	0.296
Personal history of autoimmune diseases				
Sjogren's Syndrome	1.61 (0.61, 4.27)	0.336	1.17 (0.40, 3.47)	0.771
RA	1.15 (0.14, 9.27)	0.897	1.05 (0.11, 9.97)	0.963
APS	2.54 (1.33, 4.87)	0.005	2.6 (1.21, 5.59)	0.014
Clinical domains				
Constitutional	0.98 (0.64, 1.50)	0.928	1.22 (0.74, 2.00)	0.434
Mucocutaneous	0.76 (0.41, 1.42)	0.399	0.76 (0.38, 1.51)	0.429
Musculoskeletal	1.08 (0.62, 1.88)	0.779	1.06 (0.56, 1.99)	0.859
Serosal	1.02 (0.65, 1.60)	0.924	1.18 (0.71, 1.96)	0.528
Renal	0.69 (0.45, 1.05)	0.084	0.71 (0.41, 1.23)	0.220
Neuropsychiatric	1.16 (0.63, 2.16)	0.637	0.93 (0.45, 1.93)	0.842
Hematologic	1.12 (0.70, 1.79)	0.649	0.97 (0.57, 1.65)	0.917
Immunology domains				
Anti-dsDNA, positive	0.96 (0.57, 1.60)	0.865	1.28 (0.70, 2.33)	0.422
C3, low	0.60 (0.38, 0.95)	0.030	0.86 (0.43, 1.69)	0.654
C4, low	0.59 (0.37, 0.93)	0.024	0.66 (0.34, 1.30)	0.227

*Diabetes mellitus, arterial hypertension, dyslipidemia. †Mestizo: individuals born in Latin America who had both Amerindian and white ancestors. ACR, American College of Rheumatology; anti-dsDNA, anti-double stranded deoxyribonucleic acid; RA, rheumatoid arthritis; APS; antiphospholipid syndrome; SDI, SLICC/ACR damage index; SLE, Systemic Lupus Erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SLICC, Systemic Lupus International Collaborating Clinics.

Conclusions: In the GLADEL 2.0 multi-ethnic cohort, we found that delay in diagnosis was more likely to occur in older SLE patients and it was associated with APS. Future analyses will allow us to identify the impact of delayed diagnosis on outcome of SLE patients. **References** [1.] Nieto R. Lupus 2024;33(4):340-346. [2.] Gómez-Puerta JA. Lupus 2021;28:961203320988586.

O015 / #174

Topic: ***AS20 - Precision Medicine***

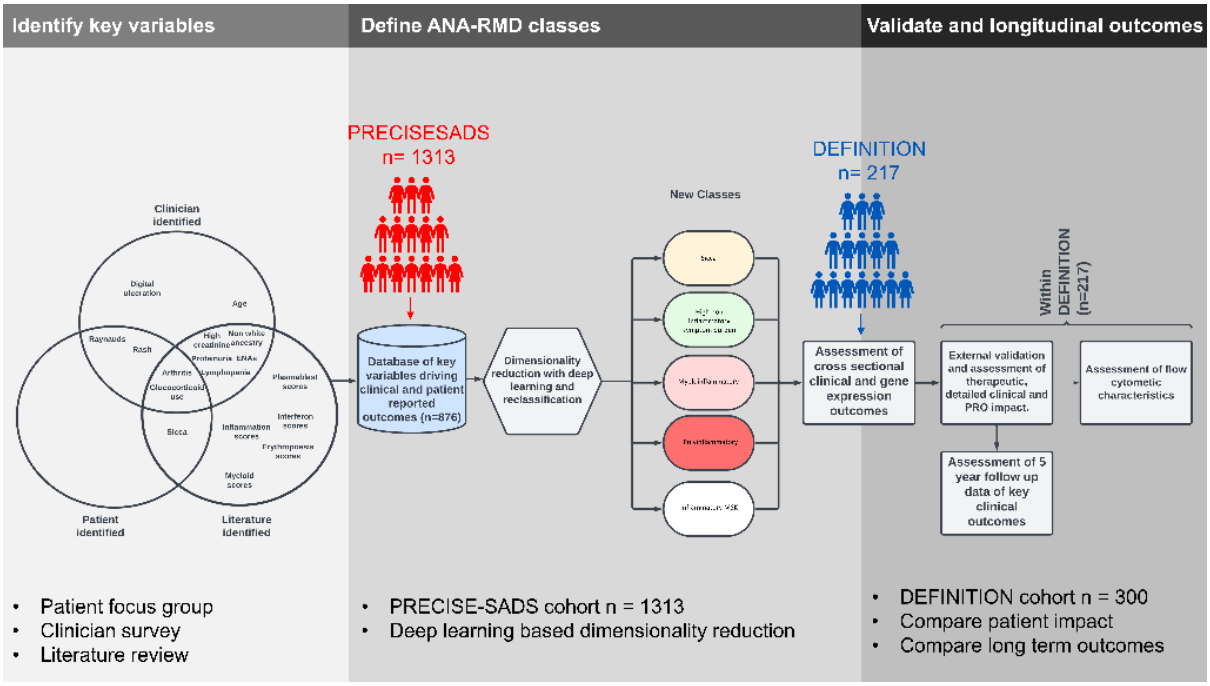
ABSTRACT CONCURRENT SESSION 02: SLE METRICS – IMPROVING OUTCOMES & MEASURES
22-05-2025 1:40 PM - 2:40 PM

DISCOVERY AND VALIDATION OF A NEW CLASSIFICATION OF ANA-RMDS THAT BETTER PREDICT LONG TERM OUTCOMES COMPARED TO LEGACY DIAGNOSES.

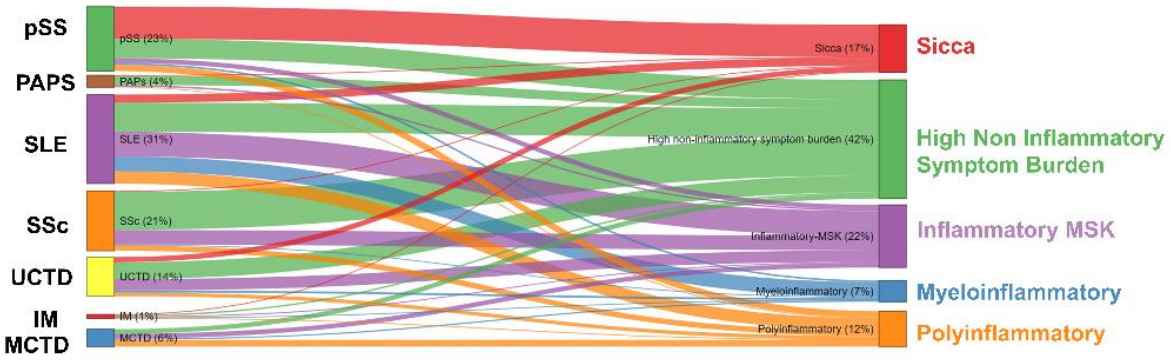
Jack Arnold[1], Lucy Marie Carter[2], Md Yuzaiful Md Yusof[2], Zoe Wigston[2], Daniel Toro Dominguez[3], Guillermo Barturen[3], Samuel Relton[4], Marta Alarcón-Riquelme[3], Edward Vital[2]
[1]Leeds Institute of Rheumatic and Musculoskeletal Medicine, Leeds, United Kingdom, [2]University of Leeds, Leeds Institute Of Rheumatic And Musculoskeletal Medicine, Leeds, United Kingdom, [3]Centre for Genomics and Oncological Resea, University Of Granada, Granada, Spain, [4]University of Leeds, Leeds Institute Of Data Analytics, Leeds, United Kingdom

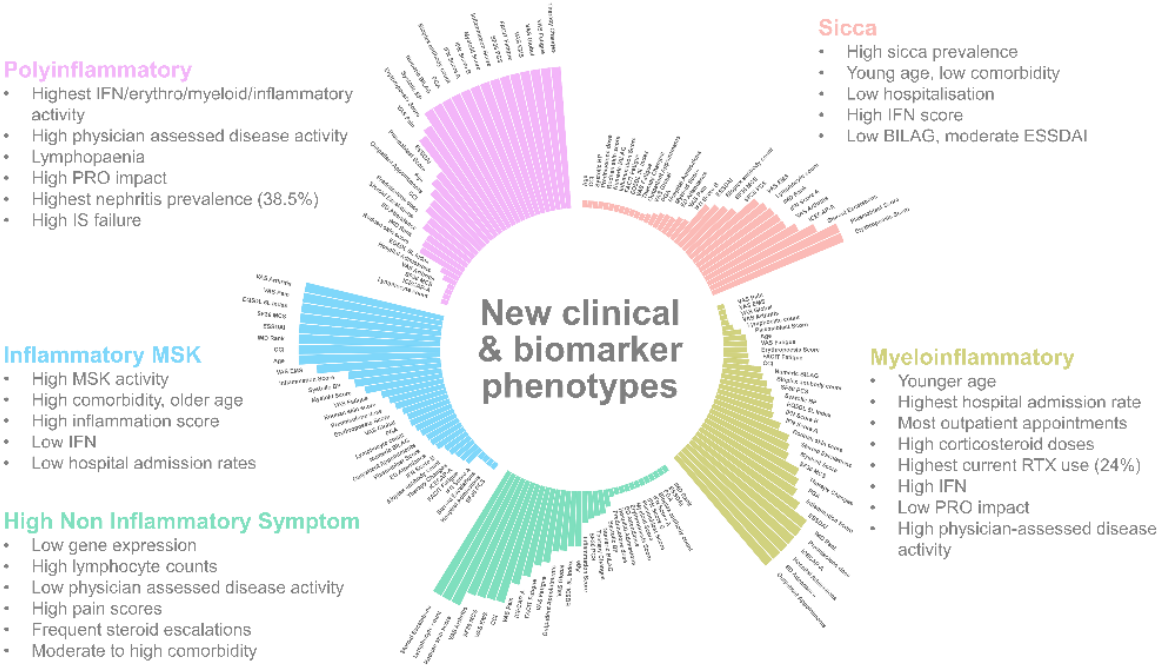
Background/Purpose: ANA-associated RMDs (ANA-RMDs) include SLE, Sjogren's, Scleroderma, Myositis, and mixed/undifferentiated CTD. Despite overlapping clinical and immunophenotypic features, there is significant disparity in access to targeted therapies across ANA-RMDs. A robust data-driven reclassification using clinical and biomarker data with clinical impact could define more homogeneous cohorts for therapies and clinical trials.

Methods: We trained a variational autoencoder with the European PRECISESADS cohort of 876 ANA-RMD patients using R, keras, and tensorflow. 25 covariates were prioritised by ANA-RMD specialists and patient focus-groups . Data was compressed to an 8-neuron latent space and analyzed with multiple clustering techniques. For validation, Kmeans centroids from PRECISESADS were applied to the DEFINITION dataset (219 patients). Cluster durability was assessed using entropy, elbow plots, and cluster stability index. Gene expression data was analyzed with heatmaps and summary statistics. Clinical impact in DEFINITION was analyzed cross-sectionally and longitudinally using descriptive statistics, PROs (e.g., SF36), physician assessments (e.g., BILAG-2004, PGA), and gene expression scores. 5-year follow-up outcomes included hospitalization rates. Kaplan-Meier and Sankey plots were generated with survival and flipPlots R packages.



Results: Deep learning revealed five distinct ANA-RMD classes. Each class encompassed patients from various legacy diagnoses, with no single legacy diagnosis mapping to a new class. These classes were: (i) Sicca, mostly patients with a legacy diagnosis of pSS, SLE, or UCTD with low disease activity but high IFN-I expression; (ii) Quiescent, characterized by low gene expression and physician-assessed disease activity but high patient-reported pain scores; (iii) Active MSK disease, with high MSK disease activity and high inflammatory gene expression; (iv) Polyinflammatory, with high levels of therapeutic change, PRO impact, and high myeloid/interferon/inflammatory gene expression, containing substantial numbers of previously undifferentiated patients; (v) Myeloinflammatory, with high healthcare utilization, physician-assessed disease activity, and emergency department attendance. Five-year healthcare data revealed significant differences in hospital admission rates ($p<0.01$) and emergency department attendance ($p<0.01$) for the new classes but not for legacy diagnoses.





Conclusions: Using advanced deep learning, we developed and validated a new classification for ANA-RMDs. Our findings showed that (i) more of the ANA-RMD spectrum could be classified than with legacy diagnoses; (ii) immunophenotypic and clinical features within these classes were more homogeneous than with legacy diagnoses, suggesting suitability for the same therapies and outcomes; (iii) these classes better predicted long-term outcomes and healthcare utilization. Clinical trials in these populations may yield larger effect sizes and provide evidence applicable to more patients, thereby reducing healthcare inequality.

O016 / #589

Topic: ***AS23 - SLE-Diagnosis, Manifestations, & Outcomes***

ABSTRACT CONCURRENT SESSION 02: SLE METRICS – IMPROVING OUTCOMES & MEASURES
22-05-2025 1:40 PM - 2:40 PM

RELIABILITY OF SLE-DAS, SLEDAI-2K, AND PGA INSTRUMENTS IN ASSESSING SLE DISEASE ACTIVITY: A STUDY AMONG GLOBAL LUPUS EXPERTS

Beatriz Mendes[1], Carolina Mazeda[2], Diogo Jesus[3,4], Carla Henriques[5,6], Ana Matos[5,7], Irene Altabás González[8], Samuel Andrade[9], Simone Appenzeller[9], George Bertsias[10,11], Ricard Cervera[12], Nathalie Costedoat-Chalumeau[13], Antonis Fanouriakis[14], Thiago Fragoso[15], Mariele Gatto[16], László Kovacs[17], Chi Chiu Mok[18], Ioannis Parodis[19,20], José María Pego-Reigosa[8], Matteo Piga[21], Anisur Rahman[22], Christopher Sjöwall[23], Maria Tektonidou[24], Zahi Touma[25], Manuel Francisco Ugarte-Gil[26], Margherita Zen[27], Andrea Doria[27], Luís Inês[1,4,28]
[1]Rheumatology Department, Centro Hospitalar Universitário de Coimbra - ULS Coimbra, Coimbra, Portugal, [2]Unidade Local de Saúde da Região de Aveiro, Rheumatology, Aveiro, Portugal, [3]Unidade Local de Saúde da Região de Leiria, Leiria, Portugal, [4]Faculty of Health Sciences, University of Beira Interior, Covilhã, Portugal, [5]Polytechnic Institute of Viseu, School Of Technology And Management, Viseu, Portugal, [6]University of Coimbra, Centre For Mathematics, Coimbra, Portugal, [7]7. Research Centre in Digital Services (CISeD), Viseu, Portugal, [8]Complejo Hospitalario Universitario de Vigo. Grupo IRIDIS. Instituto de Investigación Sanitaria Galicia Sur (IISGS), Rheumatology, Vigo, Spain, [9]University of Campinas, Department Of Orthopedics, Rheumatology, And Traumatology, Campinas, Brazil, [10]University Hospital of Heraklion, Rheumatology And Clinical Immunology, Heraklion, Greece, [11]Laboratory of Autoimmunity-Inflammation, Institute of Molecular Biology and Biotechnology, Heraklion, Greece, [12]Hospital Clinic, Autoimmune Diseases, Barcelona, Spain, [13]Université de Paris, Centre De Référence Maladies Auto-immunes Et Systémiques Rares, Service De Médecine Interne Pôle Médecine, Hôpital Cochin, Aphp, Paris, France, [14]National and Kapodistrian University of Athens Medical School, Rheumatology And Clinical Immunology Unit, 4th Department Of Internal Medicine, Attikon University Hospital, Joint Rheumatology Program, Athens, Greece, [15]Universidade Federal de Alagoas, Rheumatology Division, Faculty Of Medicine, Maceió, Brazil, [16]University of Turin, Clinical And Biological Sciences, Turin, Italy, [17]University of Szeged, Department Of Rheumatology And Immunology, Faculty Of Medicine, Szeged, Hungary, [18]Tuen Mun Hospital, Department Of Medicine, Hong Kong, China, [19]Division of Rheumatology, Department of Medicine Solna, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden, [20]Department of Rheumatology, Faculty of Medicine and Health, Örebro University, Örebro,

Sweden, [21]Università di Cagliari, Rheumatology Unit, Cagliari, Italy, [22]University College London, London, United Kingdom, [23]Department of Biomedical and Clinical Sciences, Division of Inflammation and Infection/Rheumatology, Linköping, Sweden, [24]National and Kapodistrian University of Athens, Joint Academic Rheumatology Program, Rheumatology Unit, First Department Of Propaedeutic Internal Medicine, "laiko" General Hospital, Medical School, Athens, Greece, [25]University of Toronto, Division Of Rheumatology, Department Of Medicine; Toronto Western Hospital-lupus Clinic; Institute Of Health Policy, Management And Evaluation, Toronto, Canada, [26]Grupo Peruano de Estudio de Enfermedades Autoinmunes Sistemicas, Universidad Cientifica del Sur, Lima, Peru Rheumatology Department, Hospital Guillermo Almenara Irigoyen, EsSalud, Lima, Peru, Lima, Peru, [27]Rheumatology Unit, University of Padua, Department Of Medicine, Padua, Italy, [28]University of Coimbra, Faculty Of Medicine, Coimbra, Portugal

Background/Purpose: Reliability measures the consistency of an instrument's assessments. Instruments intended for clinical and research use must exhibit high reliability. There is a need for studies that evaluate and compare the reliability of different instruments used to measure SLE disease activity. This study aims to estimate the intra-rater and inter-rater reliability of three SLE disease activity measurement tools as assessed by lupus experts: the SLE Disease Activity Score (SLE-DAS), the SLE Disease Activity Index 2000 (SLEDAI-2K), and the Physician Global Assessment (PGA). [1, 2]

Methods: A group of 19 lupus experts from 12 countries (Europe, North America, South America, and Asia) evaluated 24 clinical case vignettes of SLE covering a wide spectrum of organ manifestations and disease severity. All raters completed a training on scoring rules for SLE-DAS, SLEDAI-2K and PGA before assessing the clinical vignettes. Raters scored each clinical vignette with SLE-DAS, SLEDAI-2K, and PGA twice, with at least a 10-day interval between rounds. The clinical vignettes were randomly ordered and assessed through an online survey. Intra-rater and inter-rater reliability were assessed using the Intraclass Correlation Coefficient (ICC) and reported with 95% CI. For this analysis, ICC estimates were derived from a two-way random effects model (single rater). All calculations were performed using the Stata Statistical Software (Release 17) with the kappaetc module. The Coefficient of Variation (CV) was also used as a measure of reliability. [3] The CV was calculated for each vignette, based on the 19 measurements from each rater, for SLE-DAS, SLEDAI-2K, and PGA. Then, for each disease activity measure, the mean of the CV values across the 24 vignettes was used as a summary measure of within-subject variability and is expressed as a percentage.

Results: The 24 clinical vignettes represented a wide variety of active SLE manifestations, including skin rash (20.8%), arthritis (12.5%), renal involvement (12.5%), thrombocytopenia (12.5%), cardiac/pulmonary involvement (12.5%),

mucocutaneous vasculitis (8.3%), serositis (8.3%), and neuropsychiatric SLE (8.3%). Systemic vasculitis, myositis, alopecia, hemolytic anemia, and leukopenia were each present in 4.2% of the vignettes. Hypocomplementemia and/or positive anti-dsDNA were present in 75.0%. All the 19 lupus experts completed two rounds of assessment of the 24 clinical vignettes, totaling 912 case assessments. Scores ranged from 0.37 to 27.37 in SLE-DAS, 0 to 21 in SLEDAI-2K, and 0.0 to 3.0 in PGA. The inter-rater ICCs were 0.93, 0.91, and 0.74, and the intra-rater ICCs were 0.94, 0.93, and 0.88 for SLE-DAS, SLEDAI-2K, and PGA, respectively. The CVs (first rating round) were 8.2%, 19.7%, and 41.1% for SLE-DAS, SLEDAI-2K, and PGA, respectively. The ICCs (95% CI) and CVs for SLE-DAS, SLEDAI-2K, and PGA are detailed in tables 1 and 2.

Conclusions: This study demonstrates that both SLE-DAS and SLEDAI-2K presented good to excellent inter-rater reliability, indicating strong consistency in scoring across different experts. Notably, SLE-DAS achieved excellent intra-rater reliability, reflecting a high degree of stability in individual assessments between assessments at different times. Both SLEDAI-2K and PGA exhibited good to excellent intra-rater reliability, while PGA showed moderate to good inter-rater reliability. Furthermore, SLE-DAS exhibited the lowest within-subject variability, as evidenced by its lower CV values compared to SLEDAI-2K and PGA. **References:** Jesus D., et al. *Ann Rheum Dis* 2019;78:365-71. Piga M., et al. Lancet Rheumatol 2022;4:e441-e449. Shechtman, O. The coefficient of variation as an index of measurement reliability. In: S.A.R. Doi, G.M. Williams (Eds.)

Table 1: Inter-rater and intra-rater Intraclass Correlation Coefficient (ICC) of SLE-DAS, SLEDAI-2K and PGA.

	ICC (95% CI)	
	Inter-rater reliability	**Intra-rater reliability**
SLE-DAS	0.9252 (0.8808-0.9608)	0.9404 (0.9032-0.9685)
SLEDAI-2K	0.9096 (0.8571-0.9522)	0.9272 (0.8828-0.9612)
PGA	0.7389 (0.6175-0.8518)	0.8809 (0.8217-0.9286)

Table 2: Coefficient of Variation (CV) of SLE-DAS, SLEDAI-2K and PGA.

	CV (%)	
	1st rating round	2nd rating round
SLE-DAS	8.22	7.61
SLEDAI-2K	19.68	20.41
PGA	41.09	38.85

. Methods of clinical epidemiology 2013:39-49.

O017 / #393

Topic: ***AS07 - Cutaneous Lupus***

ABSTRACT CONCURRENT SESSION 02: SLE METRICS – IMPROVING OUTCOMES & MEASURES
22-05-2025 1:40 PM - 2:40 PM

ERYTHEMA AND SCALE INFLUENCE QUALITY OF LIFE AND IMPRESSION OF DISEASE PROGRESSION IN CUTANEOUS LUPUS PATIENTS

Grace Lu[1], Shae Chambers[2], Tyler Cepica[1], Lillian Xie[2], Rui Feng[3], Victoria P. Werth[2,4], Benjamin Chong[1]
[1]University of Texas Southwestern Medical Center, Dermatology, Dallas, United States of America, [2]University of Pennsylvania Perelman School of Medicine, Dermatology, Philadelphia, United States of America, [3]University of Pennsylvania, Center For Clinical Epidemiology And Biostatistics, Philadelphia, United States of America, [4]Corporal Michael J. Crescenz VA Medical Center,, Philadelphia, United States of America

Background/Purpose: The Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) evaluates disease activity (CLASI-A) by assessing signs including erythema and scale in patients with cutaneous lupus erythematosus (CLE). While erythema and scale have been frequently mentioned as significant signs from patient interviews, their impact on how CLE patients feel about their skin disease has not been studied in larger patient cohorts. Understanding whether erythema and/or scale are important to patients would further justify their inclusion as scoring drivers in CLASI-A.

Methods: We conducted a prospective study investigating the relationships between CLASI-A erythema and scale scores and patient-reported outcome measures (PROMs) at baseline, and changes in these scores over six months. 131 CLE patients were recruited in outpatient dermatology clinics at University of Texas Southwestern Medical Center, Parkland Health, and University of Pennsylvania between July 2018 and November 2023. Examined PROMs included the CLE Quality of Life Index (CLEQoL), Dermatology Quality of Life Index (DLQI), Patient Impression of Disease Progression (PIDP), and Analogue Pain, Itch, and Fatigue Scales (APIFS). Spearman correlation analyses were performed to examine relationships between CLASI-A erythema or scale and PROMs. To compare the degree of association between CLASI-A erythema and scale versus PROMs, Spearman's rho between erythema versus scale and PROMS were compared using paired t-test after Fisher's transformation separately at baseline and then after six months.

Results: At baseline (N = 131), CLASI-A erythema had significant correlation to all PROMs, whereas scale directly correlated to all PROMs excluding the photosensitivity domain in CLEQoL (**Table 1**). Skin health from APIFS had the strongest correlation to

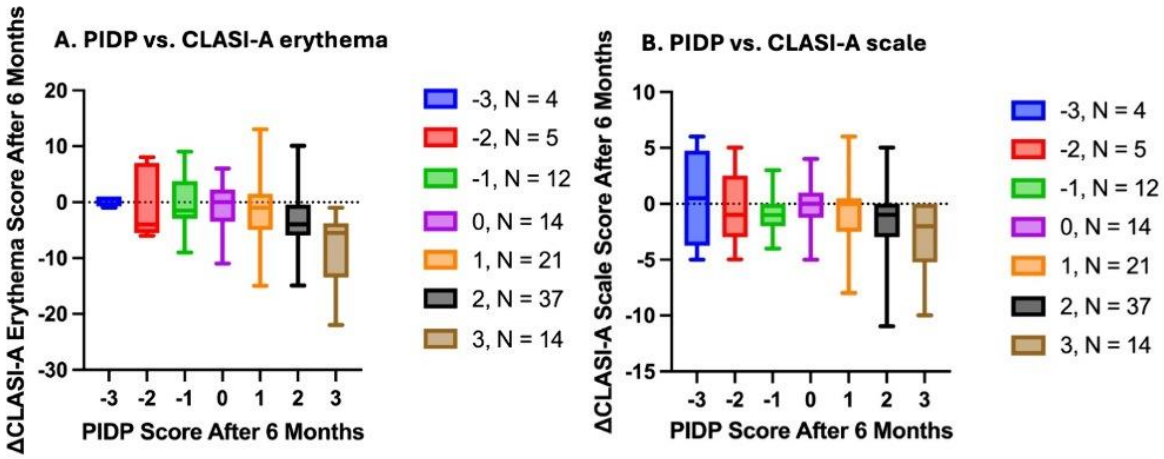
erythema (r=-0.38, p<0.01) and scale (r=-0.32, p<0.01). After six months (N = 107), PIDP scores were most notably correlated to change in erythema (ρ = -0.41, p < 0.01) and scale (r = -0.23, p = 0.02) (**Figure 1**). The association between erythema and PROMs was not statistically different from that between scale and PROMs at baseline (p = 0.42) or after six months (p = 0.22).

Table 1. Correlation Between CLASI-A Erythema and Scale vs. Patient-Reported Outcome Measures at Baseline

Patient-Reported Outcome Measure	N	Median (IQR)	Correlation with CLASI-A Erythema		Correlation with CLASI-A Scale	
			Spearman's rho	p-value	Spearman's rho	p-value
APIFS						
Pain	131	4 (1–6)	0.23	0.009	0.26	0.003
Itch	131	5 (2–8)	0.29	0.0007	0.27	0.002
Fatigue	129	5 (2–8)	0.2	0.03	0.22	0.01
Skin Health	131	5 (3–6)	-0.38	<0.0001	-0.32	0.0002
General Health	131	7 (5–8)	-0.26	0.0024	-0.25	0.008
CLEQoL						
Body Image/Cosmetic Effects	111	50 (31.3–84.4)	0.26	0.006	0.27	0.005
Photosensitivity	111	66.7 (50–100)	0.28	0.003	0.13	0.17
Functioning	131	33.3 (14.6–61.9)	0.32	0.0002	0.3	0.0004
Emotions	131	52.5 (32.5–82.5)	0.21	0.02	0.18	0.04
Symptoms	131	50 (32.1–71.4)	0.33	0.0001	0.31	0.0003
DLQI	130	9 (4–14.8)	0.37	<0.0001	0.31	0.0004

Abbreviations: APIFS: Analogue Itch, Pain, and Fatigue Scales; CLASI-A: Cutaneous Lupus Erythematosus Disease Area and Severity Index Activity Score; CLEQoL: Cutaneous Lupus Erythematosus Quality of Life Index; DLQI: Dermatology Quality of Life Index.

Figure 1. Erythema and scale are correlated to PIDP scores after six months.



Conclusions: At baseline, erythema and scale had a significant correlation to nearly all PROMs, which validate the importance of both signs in affecting CLE patient lives. We also found that changes in erythema and scale were significantly correlated to PIDP after 6 months, suggesting that erythema and scale can contribute greatly to disease progression that matter to patients. These results affirm the substantial impact of

erythema and scale in quality of life in CLE patients and demonstrate that improvement in erythema and scale can result in clinically meaningful benefit for CLE patients. They also justify the greater weighting of erythema in CLASI-A scoring, which can be responsive to treatments.

O018 / #78

Topic: ***AS19 - Patient-Reported Outcome Measures***

ABSTRACT CONCURRENT SESSION 02: SLE METRICS – IMPROVING OUTCOMES & MEASURES
22-05-2025 1:40 PM - 2:40 PM

THE SYSTEMIC LUPUS INTERNATIONAL COLLABORATING CLINICS FRAILTY INDEX (SLICC- FI) PREDICTS WORSENING LUPUS QUALITY OF LIFE (LUPUSQOL) IN THE ALMENARA LUPUS COHORT.

Anubhav Singh[1], Rocío V. Gamboa-Cardenas[2], Victor R. Pimentel-Quiroz[3], Zoila Rodriguez-Bellido[3], Cesar Pastor-Asurza[3], Risto Perich-Campos[3], Graciela S. Alarcón[4], Manuel Francisco Ugarte-Gil[3]
[1]Baptist Hospitals os Southeast Texas, Internal Medicine, Beaumont, United States of America, [2]Universidad Científica del Sur, Rheumatology, Lima, Peru, [3]Hospital Guillermo Almenara Irigoyen. EsSalud., Rheumatology, Lima, Peru, [4]Marnix E. Heersink School of Medicine, Rheumatology, Birmingham, United States of America

Background/Purpose: The SLICC-FI was developed to ascertain frailty in lupus patients. The aim of this study was to evaluate the SLICC- FI as a predictor of quality of life in patients from a prevalent Latin American Mestizo lupus cohort.

Methods: Patients from a single-center lupus cohort were included in these analyses. Health-related quality of life was ascertained with the LupusQoL. Frailty was ascertained using the SLICC- FI. Results are shown as mean and standard deviation or number and percentages, as appropriate. Generalized estimating equations were performed, using each domain of the LupusQoL as an outcome in the subsequent visit and the SLICC- FI (as a continuous variable) in the previous visit. Alternative analyses were also carried out including the SLICC- FI as a categorical variable (robust, less fit, least fit, and frail). In both approaches, the multivariable models were adjusted for possible confounders (age at diagnosis, gender, socioeconomic status, ethnicity, Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2K), Systemic Lupus Erythematosus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR DI), disease duration at baseline, prednisone daily dose, antimalarial and immunosuppressive drug use, and the same domain the LupusQoL in the previous visit). Statistical significance was $p<0.05$.

Results: Four-hundred and twenty-eight patients and 2645 visits were included in the study, these patients were followed for 4.71 (3.52) years; 392 (91%) were women and the age of diagnosis was 35.2 (13.4) years. At baseline, the disease duration was 7.2 (6.6) years, while SDI and SLICC-FI score were 1.0 (1.3) and 0.17 (0.05), respectively. Sixty-two patients (14.7%) were classified as frail, 325 (77.0%) were classified as least

fit, 35 (8.3%) were classified as less fit, and no patient was classified as robust. The mean of the LupusQoL domains for physical function was 66.5 (23.8), for pain 67.9 (26.6), for planning 69.3 (28.9), for intimate relationship 58.6 (35.4), for burden to others 50.4 (31.2), for emotional health 64.9 (24.7), for body image 61.5 (25.8), and for fatigue 60.6 (26.5). In the main analyses, after adjusting for possible confounders, the SLICC- FI scores continued to predict worse LupusQoL in the physical function, pain, planning, and emotional health domains; these data are depicted in Table 1. In the alternative analyses, frail and least fit categories predicted worse LupusQoL in the domains of physical function, pain, and planning; in turn, frail predicted worse fatigue, compared to less fit, after adjustment by possible confounders; these data are depicted in Table 2.

Table 1: The predictive value of the SLICC-FI (as a continuous variable) on HRQoL in SLE patients

	Unadjusted Model		Adjusted Model*	
	B (SE)	*p value*	B (SE)	*p* value
Physical function	-8.94 (0.90)	<0.001	-1.86 (0.50)	<0.001
Pain	-7.28 (1.04)	<0.001	-2.54 (0.72)	<0.001
Planning	-7.24 (1.07)	<0.001	-2.30 (0.67)	<0.001
Intimate relationship	-7.08 (1.40)	<0.001	-2.21 (1.07)	0.039
Burden to others	-4.89 (1.14)	<0.001	-1.44 (0.75)	0.055
Emotional health	-3.71 (1.02)	<0.001	-1.20 (0.53)	0.025
Body image	-3.45 (1.08)	0.001	-1.35 (0.82)	0.100
Fatigue	-3.54 (1.06)	<0.001	-0.99 (0.57)	0.085

* Adjusted for age at diagnosis, gender, socioeconomic status, ethnicity, SLEDAI-2K, SDI, disease duration at baseline, prednisone daily dose, antimalarial and immunosuppressive drug use, and the same domain the LupusQoL in the previous visit.

Table 2: The predictive value of the SLICC-FI (as a categorical variable) on HRQoL in SLE patients

	Unadjusted model				Adjusted model*			
	Frail#		Least fit#		Frail#		Least fit#	
	B (SE)	*p value*	B (SE)	*p value*	B (SE)	*p value*	B(SE)	*p value*
Physical function	-27.91 (3.09)	<0.001	-10.29 (1.54)	<0.001	-3.26 (1.50)	0.030	-1.87 (0.83)	0.024
Pain	-23.30 (3.50)	<0.001	-9.29 (1.75)	<0.001	-6.43 (2.12)	0.002	-3.18 (1.08)	0.003
Planning	-23.02 (3.58)	<0.001	-9.79 (1.96)	<0.001	-5.13 (2.04)	0.012	-2.60 (1.13)	0.022
Intimate relationship	-21.37 (4.89)	<0.001	-6.20 (3.49)	0.076	-3.48 (3.34)	0.297	0.69 (2.34)	0.767
Burden to others	-16.16 (3.78)	<0.001	-5.45 (2.66)	0.041	-3.09 (2.36)	0.191	-0.17 (1.59)	0.916
Emotional health	-13.83 (3.23)	<0.001	-4.62 (1.91)	0.016	-3.84 (1.78)	0.007	-1.99 (1.10)	0.070
Body image	-11.58 (3.81)	0.002	-5.96 (2.72)	0.028	-2.97 (2.73)	0.278	-1.38 (1.85)	0.457
Fatigue	-12.13 (3.59)	<0.001	-4.67 (2.49)	0.061	-3.34 (1.82)	0.067	-2.37 (1.28)	0.065

#In this model, the category less frail was included as the reference group. * Adjusted for age at diagnosis, gender, socioeconomic status, ethnicity, SLEDAI-2K, SDI, disease duration at baseline, prednisone daily dose, antimalarial and immunosuppressive drug use, and the same domain the LupusQoL in the previous visit

Conclusions: The SLICC-FI predicts worse HRQoL as measured by LupusQoL in a prevalent Latin-American lupus cohort, supporting the relevance of this index in the evaluation of these patients.

O019 / #487

Topic: *AS07 - Cutaneous Lupus*

ABSTRACT CONCURRENT SESSION 03: INNATE AND ADAPTIVE IMMUNITY IN SLE
22-05-2025 1:40 PM - 2:40 PM

CD38 IS OVEREXPRESSED BY IMMUNE CELLS IN CUTANEOUS LUPUS SKIN

Grace Lu[1], Kangyi Zhang[1], Grant Barber[2], Richard Wang[1], Benjamin Chong[1]
[1]University of Texas Southwestern Medical Center, Dermatology, Dallas, United States of America, [2]Sam Houston State University College of Osteopathic Medicine, Conroe, United States of America

Background/Purpose: Cutaneous lupus erythematosus (CLE) is an autoimmune skin disease in which metabolic abnormalities may drive immune dysregulation. An unbiased LC/MS metabolomics study showed dysregulation of nicotinamide adenine dinucleotide (NAD) metabolism in the skin of CLE patients compared to healthy controls. CD38 is a multifunctional transmembrane enzyme that plays an important role in NAD metabolism and has become an emerging therapeutic target in the treatment of systemic lupus erythematosus (SLE).[1] However, CD38 expression in CLE has not been well characterized. [1.] Ostendorf L., Burns M., Ostendorf L., Durek P., Heinz G., Heinrich F., Garantziotis P., Enghard P., Richter U., Biesen R., Schneider U., Knebel F., Burmester G., Radbruch A., Mei H., Mashreghi M., Hiepe F., Alexander T. N Engl J Med 2020;383(12):1149-1155.

Methods: We sought to investigate whether CD38 expression was altered in CLE lesional skin and identify the immune cell populations overexpressing CD38. Skin samples were obtained from CLE patients and normal controls seen at outpatient dermatology clinics at the University of Texas Southwestern Medical Center and Parkland Health. To compare the levels of CD38 expression between CLE versus normal skin, RNA levels were assessed by quantitative RT-PCR (qRT-PCR) from 16 CLE lesion skin biopsies and 11 control skin samples, and protein expression was assessed by immunohistochemistry on 7 CLE lesion skin biopsies and 4 control skin samples. Immunofluorescence double staining of CD38 with CD3, CD20, and CD68 was performed using 5 CLE lesion skin biopsies and 5 control skin samples to examine CD38 expression of candidate immune cell populations, including T-cells (CD3), B-cells (CD20), and monocytes (CD68), respectively. Manders' coefficients M1 and M2 were determined to examine the extent of overlap between CD38 and CD3, CD20, and CD68 expression.

Results: qRT-PCR revealed a significant upregulation of CD38 expression in CLE patients versus controls (median log2 fold change of 6.56 vs -0.48, $p<0.0001$). Immunohistochemical staining of CD38 in 7 lesional and 4 normal skin samples

revealed a significantly higher number of CD38⁺ cells in CLE skin (median: 2105.8 cells/mm2, IQR: 1164.9-2980.0) compared to normal skin (median: 238.5 cells/mm2, IQR: 181.5-426.8, p=0.02) (Figure 1). Immunofluorescence co-staining for CD38 revealed significantly increased CD3⁺ cells expressing CD38 in perifollicular regions (p<0.01) and CD68⁺ cells expressing CD38 in dermal-epidermal junctions (p<0.05) in CLE skin versus normal skin, whereas CD20⁺ cells were not demonstrated to have significantly increased CD38 expression (Figure 2).

Figure 1

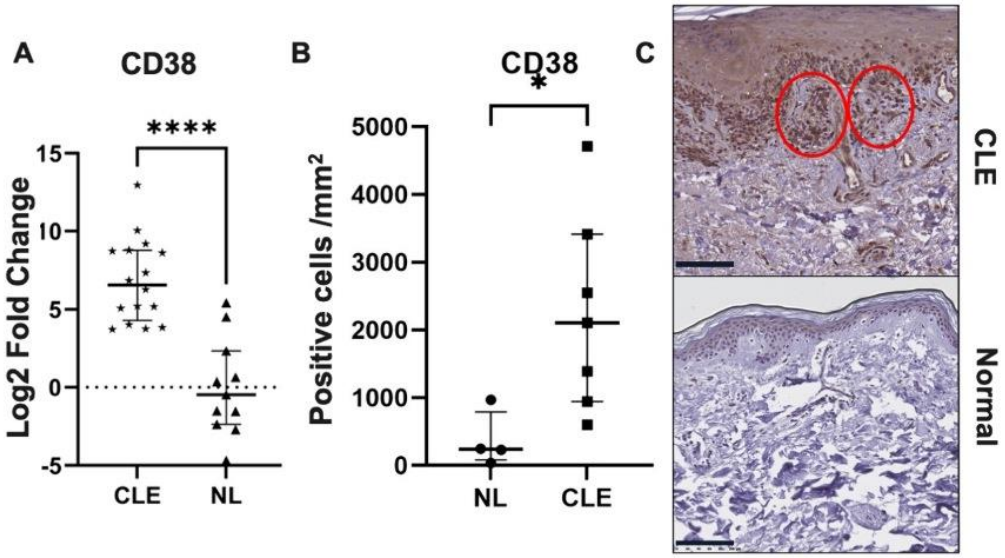
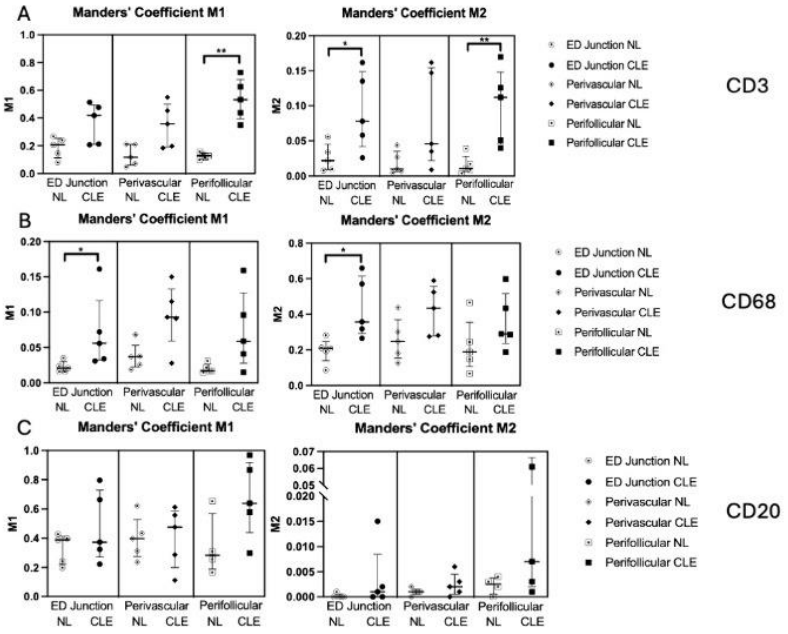


Figure 2



Conclusions: qRT-PCR and immunohistochemical staining revealed that CD38 is significantly upregulated in lesional CLE skin, which supports our metabolomics data implying dysregulation of NAD⁺ metabolism in CLE skin. In accordance with prior

studies examining immune profiles of SLE,[2] immunofluorescence double staining demonstrated CD38 overexpression in a wide range of leukocytes, including T-cells and monocytes. These findings support CD38 as a promising therapeutic target in patients with CLE. [2.] Burns M., Ostendorf L., Biesen R., Grutzkau A., Hiepe F., Mei H., Alexander T. Int J Mol Sci 2021;22(5):2424.

O020 / #593

Topic: ***AS16 - Lupus Nephritis-Pathogenesis***

ABSTRACT CONCURRENT SESSION 03: INNATE AND ADAPTIVE IMMUNITY IN SLE
22-05-2025 1:40 PM - 2:40 PM

CHARACTERIZING IMMUNE CELL SUBSETS AND INTERFERON IN THE KIDNEYS OF SLE PATIENTS

Sabah Kahnemuyipour[1], Joan Wither[1,2], Laura Whittall-Garcia[2], Rohan John[3], Zahi Touma[2], Ben Wang[3], David Brooks[1,3], Ana Konvalinka[3,4], Maya Allen[3,4], Fadi Kharouf[5]
[1]University of Toronto, Department Of Immunology, Toronto, Canada, [2]Schroeder Arthritis Institute, Toronto Western Hospital, University Health Network, Toronto, Canada, [3]University Health Network, Toronto, Canada, [4]University of Toronto, Institute Of Medical Sciences, Toronto, Canada, [5]University of Toronto Lupus Clinic, Toronto, Canada

Background/Purpose: Objectives: 20-65% of patients with systemic lupus erythematosus (SLE) will develop lupus nephritis (LN), with up to 30% failing to respond to standard immunosuppressive therapy. These patients are at risk of kidney functional decline, highlighting the need for biomarkers that predict therapeutic response at flare onset. One potential biomarker is interferon-induced gene (IFI-G) expression. Higher levels of IFI-G expression in the peripheral blood have been associated with a more severe disease course and transcriptomic studies suggest that higher IFI-G expression in renal cells is associated with a poor response to conventional treatment. However further validation is required, and it remains unclear whether the poor outcomes in patients with high IFI-G expression in their kidneys are due to the direct effects of interferon on renal cells or indirectly through recruitment of inflammatory cells. In this study, we optimized a panel of antibodies for imaging mass cytometry (IMC) enabling examination of IFI-protein (P) expression and its association with immune cells infiltration and disruption of kidney architecture in archived renal biopsies for LN patients.

Methods: Paraffin embedded renal biopsies from patients with LN who were part of the Lupus Nephritis New Emerging Team and University of Toronto Lupus Clinic cohorts were available for testing. We have previously demonstrated that IFI-P levels in the peripheral blood strongly correlate with IFI-G expression, suggesting that antibodies against IFI-Ps (ISG15, MX1, PKR) are reliable surrogates for gene expression. To facilitate standardization, a pseudo-tissue was created from peripheral blood that was composed of a mixture of IFN-stimulated and unstimulated peripheral blood mononuclear cells from a healthy control. This was subsequently mixed with plasma, clotted, and embedded in paraffin. This pseudo-tissue served as both a positive and negative control for IFI-P expression. In addition to renal biopsies, archived lymph node

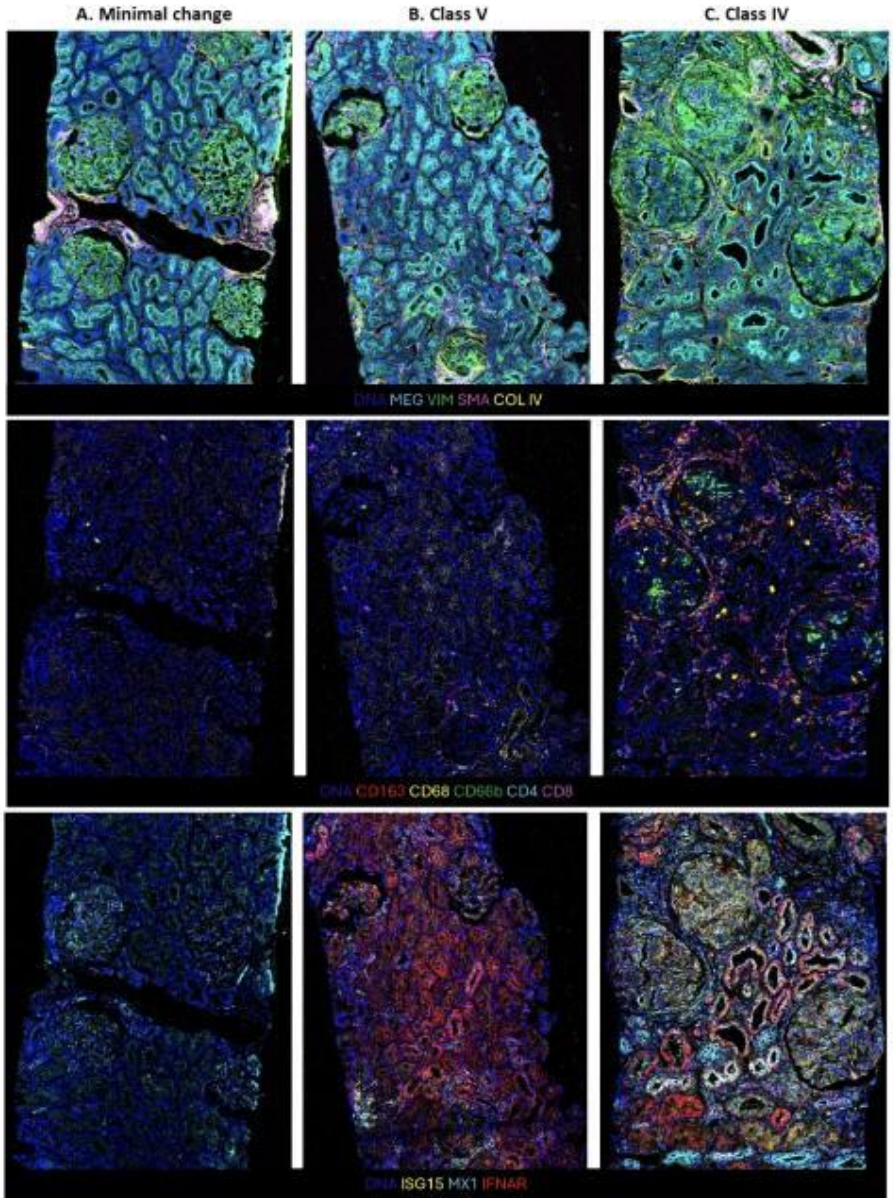
and tonsil tissues were stained to facilitate titration of antibodies directed against immune subsets.

Results: A panel of 25 metal-conjugated antibodies was successfully created that enabled staining renal resident cells/structure, infiltrating immune cells (including T cells, B cells, plasma cells, monocytes, macrophages, and dendritic cells), and IFI-Ps.[1] Testing in the pseudo-tissue confirmed that the antibodies directed against IFI-Ps (MX1, ISG15, PKR) effectively discriminated between IFN-stimulated and unstimulated cells, with a low staining background and that this tissue could be used for batch standardization for subsequent staining of a larger number of LN biopsies over time. In our preliminary studies, staining of three kidney biopsies revealed distinct patterns: with the minimal change biopsy showing no cellular infiltration and minimal expression of IFI-Ps; the membranous LN biopsy showing increased IFNAR levels but similar IFI-P expression to the minimal change biopsy and few immune cells; and the proliferative LN biopsy showing high levels IFI-Ps and many immune cells in the glomerulus and proximal tubules.[2]

Table 1. Validated IMC Panel

VIMENTIN	fibroblasts, pericytes
MEGALIN	proximal tubule
NESTIN	Podocyte
SMA	smooth muscle
COLLAGEN IV	basement membrane, fibrosis
EGFR	ubiquitously expressed
CD31	smooth endothelium
Ki67	regenerating tubular cells
CD45	hematopoietic cells
CD20	B lymphocyte
CD3	T lymphocyte
CD4	helper T cell
CD8	cytotoxic T cell
FOXP3	regulatory cell
CD11c	dendritic cells (DC)
CD163	inflammatory DC/monocyte
CD14	inflammatory DC/monocyte
CD16	inflammatory DC/monocyte
CD66b	granulocyte
CD68	macrophage
CD38	plasma cells
MX1	IFN-induced protein
ISG15	IFN-induced protein
PKR	IFN- induced protein
IFNAR1	Type I IFN receptor
HISTONE H3	Nucleus
DNA intercalator	Nucleus
DNA intercalator	Nucleus
ICSK1	Segmentation antibody
ICSK2	Segmentation antibody
ICSK3	Segmentation antibody

Figure 1. Comparative IMC staining of adult renal biopsies with minimal change disease (A), class V LN (B) and class IV LN (C). The 3 IMC images for each sample represent images obtained from the same region and time, with a selection of glomerular, tubular and stromal markers shown in the upper panels, immune markers shown in the middle panels and IFI-P and IFNAR1 in the lower panels. MEG, megalin; VIM, vimentin; aSMA, a-smooth muscle actin; COL IV, collagen IV.



Conclusions: This study validated an IMC approach for spatial analysis of interferon signatures and immune cell infiltration in LN kidney biopsies. Future analyses will apply this panel to a broader cohort of LN samples to identify biomarkers associated with treatment response. By enabling early stratification of LN patients, this approach could support the development of targeted therapies for individuals who are less likely to respond to standard treatments, ultimately improving long-term renal outcomes.

O021 / #624

Topic: ***AS22 - SLE Heterogeneity***

ABSTRACT CONCURRENT SESSION 03: INNATE AND ADAPTIVE IMMUNITY IN SLE
22-05-2025 1:40 PM - 2:40 PM

INTERFERON-INDUCED PROTEIN EXPRESSION IN THE PERIPHERAL BLOOD IMMUNE POPULATIONS OF SLE PATIENTS AT A SINGLE-CELL LEVEL: ASSOCIATION WITH CELLULAR ACTIVATION, TRAFFICKING MOLECULES, AND DISEASE ACTIVITY

Zoha Faheem[1], Giselle Boukhaled[2], Carol Nassar[1], Kieran Manion[3], Carolina Munoz-Grajales[3], Michael Kim[3], Dafna D Gladman[4], Murray Urowitz[3], Zahi Touma[5], David Brooks[2], Joan Wither[6]
[1]UofT/UHN, Immunology, Toronto, Canada, [2]Princess Margaret Cancer Centre, UHN, Toronto, Canada, [3]UHN, Toronto, Canada, [4]Krembil Research Institute, Toronto Western Hospital, Toronto, Canada, [5]University of Toronto Lupus Clinic, Division of Rheumatology, Schroeder Arthritis Institute, Krembil Research Institute, University Health Network, Toronto, Canada, [6]Schroeder Arthritis Institute, Toronto Western Hospital, University Health Network, Toronto, Canada

Background/Purpose: High levels of peripheral blood interferon (IFN)-induced gene (IIG) expression are a characteristic feature of SLE and associated with an increased risk of flare. However, how these global changes correlate with those in individual immune populations and act to promote flares remains unclear. To address this question, we examined the IFN-induced immune changes in SLE patients at a single cell level.

Methods: A 40-marker CyTOF panel was used to measure IFN-induced protein (IIP) levels in the peripheral blood immune populations of 15 healthy controls (HC), 26 quiescent (clinical SLEDAI-2K = 0 for one year), and 42 recently flaring (clinical SLEDAI-2K ≥ 1 requiring an escalation of therapy) SLE patients.

Results: Twenty-nine immune populations were identified (Figure 1A). The mean IIP levels in all populations strongly correlated with global IIG expression, and were higher in flaring than quiescent patients (Figure 1B, C). Despite this correlation, there was significant heterogeneity in IIP expression between and within the cell subsets of individual patients, with the highest median levels of IIP seen in monocytes, plasmablast/plasma cells, and activated double positive T cells. These differences paralleled the response of these populations to exogenous IFN in HC cells in-vitro. Within each cell subset of individual patients, there was a variably broad distribution of IIP expression, sometimes with distinct peaks (Figure 1D). To assess the factors contributing to this heterogeneity, we performed an analysis of extremes comparing the top and bottom 10% of IIP expressing cells in each subject (Figure 2A). Although the top IIP expressing cell subset of most populations had elevated levels of activation markers,

such as Ki67, CD86, TLR7, TLR9, and HLA-DR, these molecules were induced by IFN in vitro, suggesting that IFN plays a direct role in their upregulation in vivo (Figure 2B). Notably, increased levels of the trafficking markers were also seen in the high IIP expressing cell subset, but with the exception of β7 (an integrin implicated in homing and retention in the gut), were not induced by IFN in-vitro. Furthermore, these trafficking molecules demonstrated distinct patterns of expression, suggesting that these cells had transited different tissues. Longitudinal analysis of IIP expression over time revealed relatively stable levels despite changes in disease activity, and although the levels of IIP in the different cell subsets tended to correlate with each other, only the levels within B cells were associated with sustained or recurrent disease activity 1 year later.

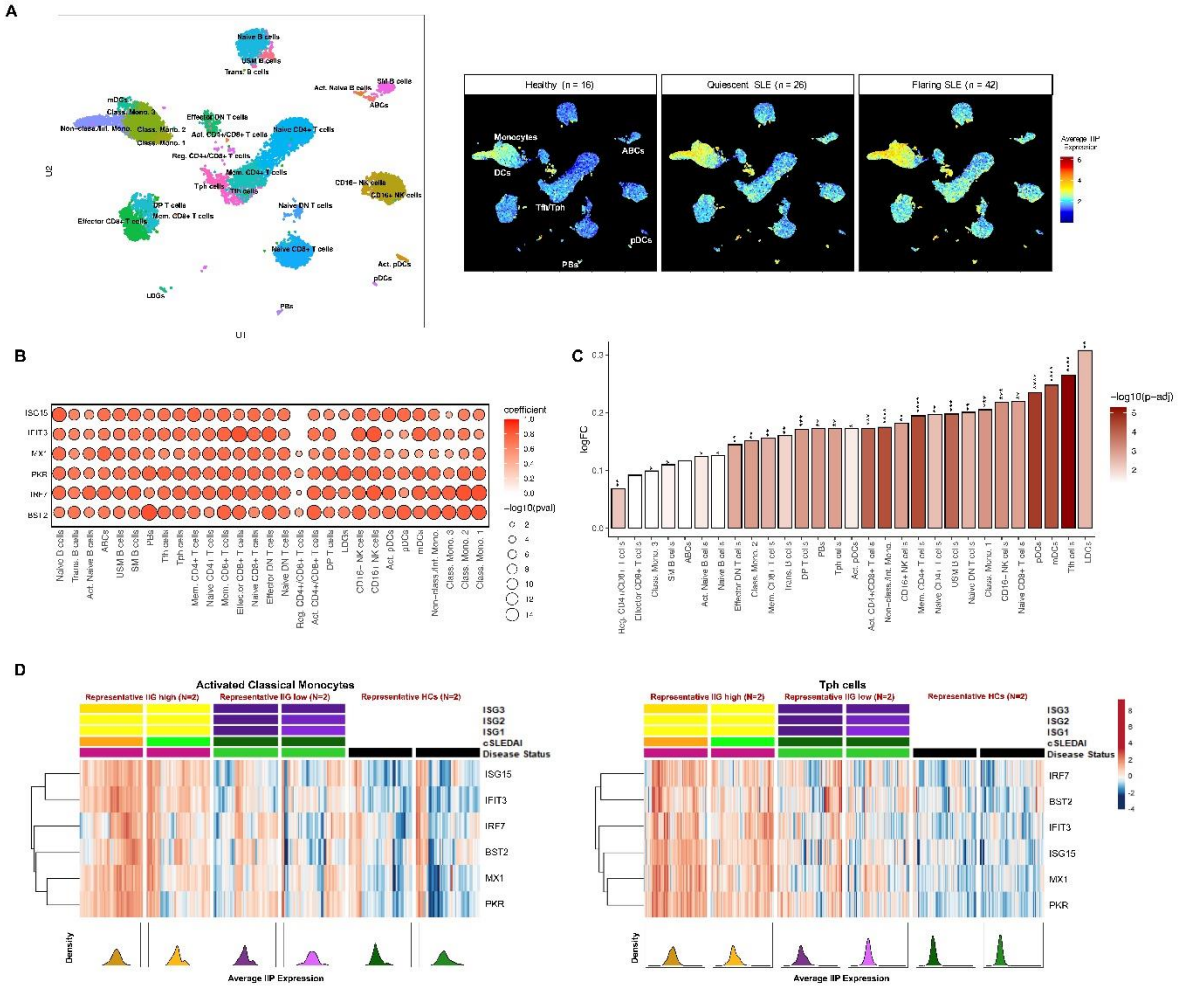


Figure 1. A) UMAP of the individual cell types showing their differential abundance and relatedness, as well as the average of 6 IIPs in HCs, quiescent and flaring patients: 29 cell types were identified based on their expression of the markers in our panel. There is a gradient in expression of average IIP expression in most cell types from low to high in HCs, quiescent patients, and flaring patients.

B) Correlation matrix in all cells: Correlation between IIP expression (shown on the y axis) and IIG expression in individual cell populations (shown on the x axis). R values are denoted by colour, and p values by the size of the dots.

C) Immunologic differences in IIP expression in immune cell populations comparing flaring and quiescent patients: Waterfall plot showing the differential levels of IIP scores between flaring and quiescent, with bars above the line indicating increased expression in SLE patients. 27/29 immune cell subsets have significantly higher IIP scores in flaring patients relative to quiescent.

D) Heterogeneity in IIP expression levels within the cell subsets of individual patients and HCs: Patients were separated into IIG high and low groups based on the top and bottom 15% of IIG score. Regardless of IIG group, there was heterogeneity in the IIP signature on a single cell level that was found within patient cells. Myeloid cells had the most marked heterogeneity, followed by T cells and then B cells.

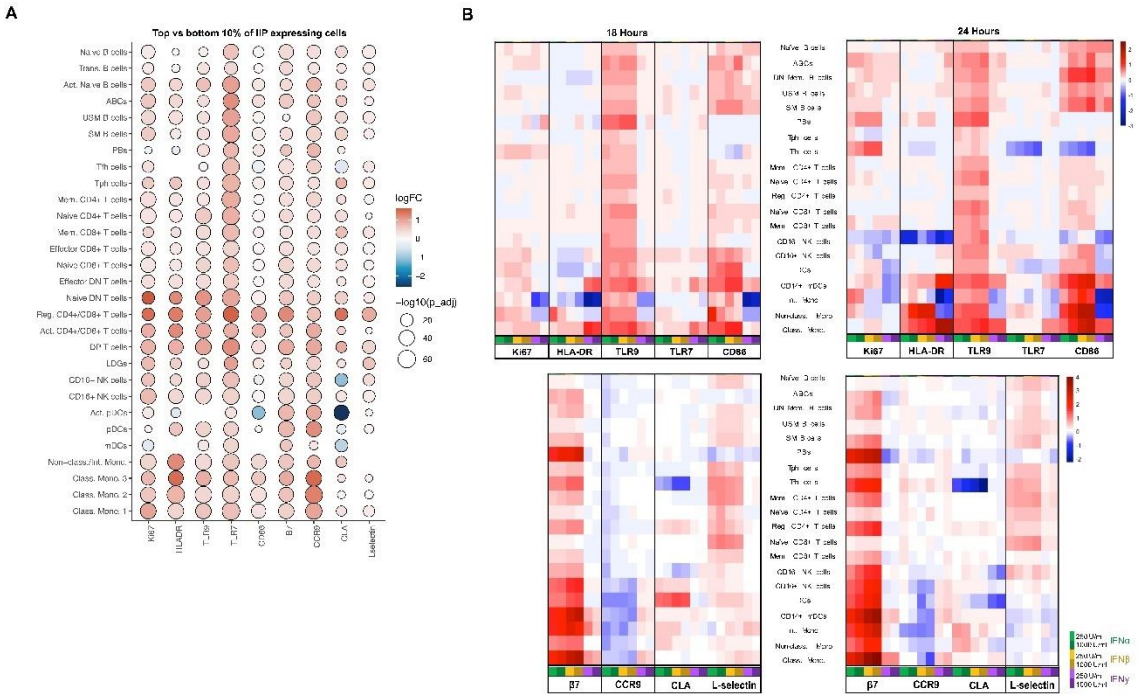


Figure 2. A) Analysis of extremes. Comparing the top and bottom 10% of IIP expressing cells within the same HCs and patients from ex vivo samples, it was found that certain activation and trafficking markers are upregulated in the IIP high cells, some of which are directly induced by IFN. R values are denoted by colour, and p values by the size of the dots.

B) Incubation with IFNα and IFNβ induces several of the cellular markers that are associated with increased IIP expression in-vitro. PBMCs from healthy controls were stimulated with the indicated IFNs for 18 or 24 hours in the presence of Golgi-Stop for the last 2 hours. Shown are fold increases relative to unstimulated control.

Conclusions: Although the mean IIP expression in each immune population correlates strongly with the IFN signature, there is significant heterogeneity between and within the cell populations of each patient in IIP expression. This appears to result not only from variability in the cells capacity to respond to IFN, but also variable exposure to IFN as cells traffic through the body.

O022 / #466

Topic: ***AS14 - Innate Immunity***

ABSTRACT CONCURRENT SESSION 03: INNATE AND ADAPTIVE IMMUNITY IN SLE
22-05-2025 1:40 PM - 2:40 PM

ALTERATIONS IN INNATE IMMUNE POPULATIONS DURING SYSTEMIC AUTOIMMUNE RHEUMATIC DISEASE DEVELOPMENT

Carmen Ucciferri[1,2], Carol Nassar[1,2], Sindhu Johnson[2], Zahi Touma[3,4,5], Zareen Ahmad[3], Dennisse Bonilla[2], Linda Hiraki[6], Arthur Bookman[2,3], Joan Wither[1,2]
[1]University of Toronto, Department Of Immunology, Toronto, Canada, [2]Schroeder Arthritis Institute, Toronto Western Hospital, Toronto, Canada, [3]University of Toronto, Toronto, Canada, [4]University Health Network, Toronto, Canada, [5]University of Toronto Lupus Clinic, Division of Rheumatology, Schroeder Arthritis Institute, Krembil Research Institute, University Health Network, Toronto, Canada, [6]The Hospital for Sick Children, Rheumatology, Toronto, Canada

Background/Purpose: Systemic autoimmune rheumatic diseases (SARD) are a group of chronic diseases characterized by the presence of anti-nuclear antibodies (ANAs). However, ANAs cannot reliably be used as a diagnostic tool because a subset of healthy women are ANA$^+$ (~20%) and the majority of these individuals will not progress to SARD. Why some individuals progress while others remain asymptomatic is unknown. Previous work suggests that monocytes/DCs may support immunological disturbances observed in SARD, including a shift toward a T helper (Th) 17 cell phenotype with a concurrent decrease in Tregs. Our objective is to evaluate functional alterations in innate immune populations during SARD development.

Methods: Experiments have been completed to examine the composition of innate immune cells in PBMCs using CITE-Seq. Samples were used from 5 ANA$^-$ healthy controls, 11 ANA$^+$ asymptomatic (5 progressors sampled prior to progression, 6 non-progressors) and 8 early SARD patients (4 SLE, 4 Sjogren's disease). Five million freshly thawed PBMCs were depleted of T and B cells by negative selection, and stained with a panel of oligo-conjugated antibodies for the identification of DC/monocyte populations. 9000 cells were sequenced at a depth of 50000 reads for gene expression and 5000 reads for CITE-Seq.

Results: Using both gene and surface protein expression, we identified 11 distinct DC and monocyte populations [Fig 1A]. Proportional analysis revealed an expansion of non-classical and activated non-classical monocytes in progressor and SARD patients [Fig 1B]. SARD patients also exhibited higher proportions of cDC3s, VCAN+ monocytes and MME+ DCs than ANA$^+$ individuals regardless of progression status [Fig 1B], suggesting a role for these cells in active disease. Comparing asymptomatic ANA$^+$ individuals, we

found that classical, intermediate, and non-classical monocytes were expanded in progressors while cDC1s, cDC2s and pDCs were expanded in non-progressors [Fig 1B]. Differential analysis showed high expression of interferon (IFN) stimulated genes in progressors and SARD patients [Fig 1C], implicating these pro-inflammatory cytokines in the transition to SARD. Interestingly, non-progressors exclusively had elevated expression of heat shock proteins [Fig 1C], which have been shown to promote immunologic tolerance and may play a role in preventing progression to SARD. In contrast, progressors had elevated HLA expression [Fig 1C], suggesting enhanced antigen presentation capacity. These differences in gene expression were observed across cell types, but intermediate monocytes are shown as representative cells due to their role in antigen presentation. Several genes were differentially expressed between progressors and SARD [Fig 1C], potentially highlighting distinct roles for genes in initiating and driving disease. Further analysis will be done to examine pathways associated with these genes.

Conclusions: Conclusion: Our data reveals differences in proportions and gene expression between progressors, non-progressors and SARD patients. Importantly, ANA^+ progressors show expanded monocyte populations and functional differences compared to non-progressors prior to progression, highlighting immune disturbances even in the asymptomatic, pre-clinical stage of SARD. The results provide insight into the immune mechanisms that drive progression from asymptomatic autoimmunity to disease in SARD.

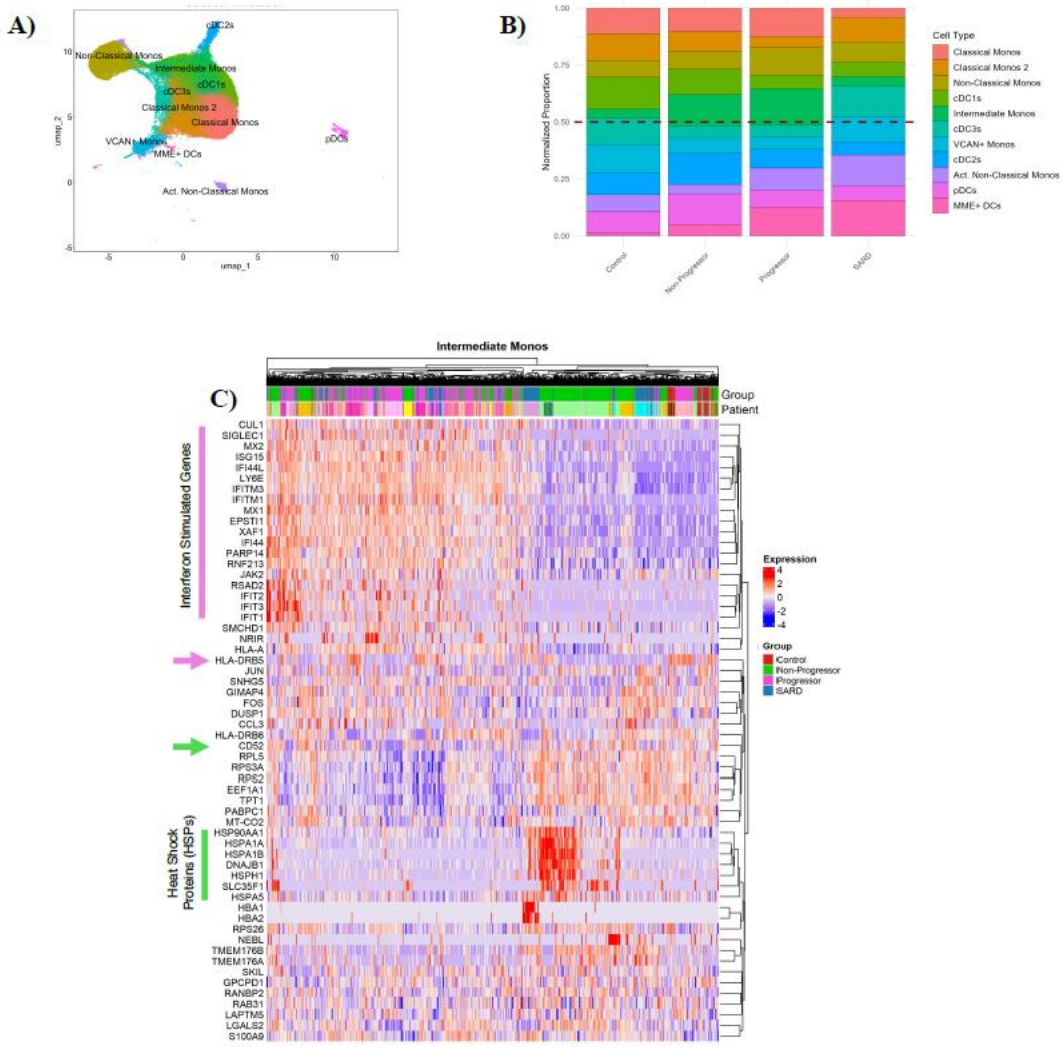


Figure 1. A) UMAP of 11 annotated monocyte and DC clusters. **B)** Proportional analysis showing each cluster for control, non-progressor, progressor and SARD groups. Data was normalized to account for differences in cell counts per cluster and per patient sample. **C)** Heatmap showing differentially expressed genes between patient groups, with intermediate monocytes as a representative cell cluster (log2FC = |1.0|, Q > 0.05, min.pct = 0.1). Similar trends were seen in the remaining cell types. Genes and patients were clustered in an unsupervised manner. Genes of interest are indicated with pink representing genes elevated in progressors and green representing genes elevated in non-progressors.

O023 / #182

Topic: ***AS14 - Innate Immunity***

ABSTRACT CONCURRENT SESSION 03: INNATE AND ADAPTIVE IMMUNITY IN SLE
22-05-2025 1:40 PM - 2:40 PM

NEUTROPHIL EXTRACELLULAR TRAPS ARE SUFFICIENT TO ACTIVATE THE ALTERNATIVE PATHWAY OF COMPLEMENT, WHICH IS CONSTITUITIVELY ACTIVE IN HUMAN SLE

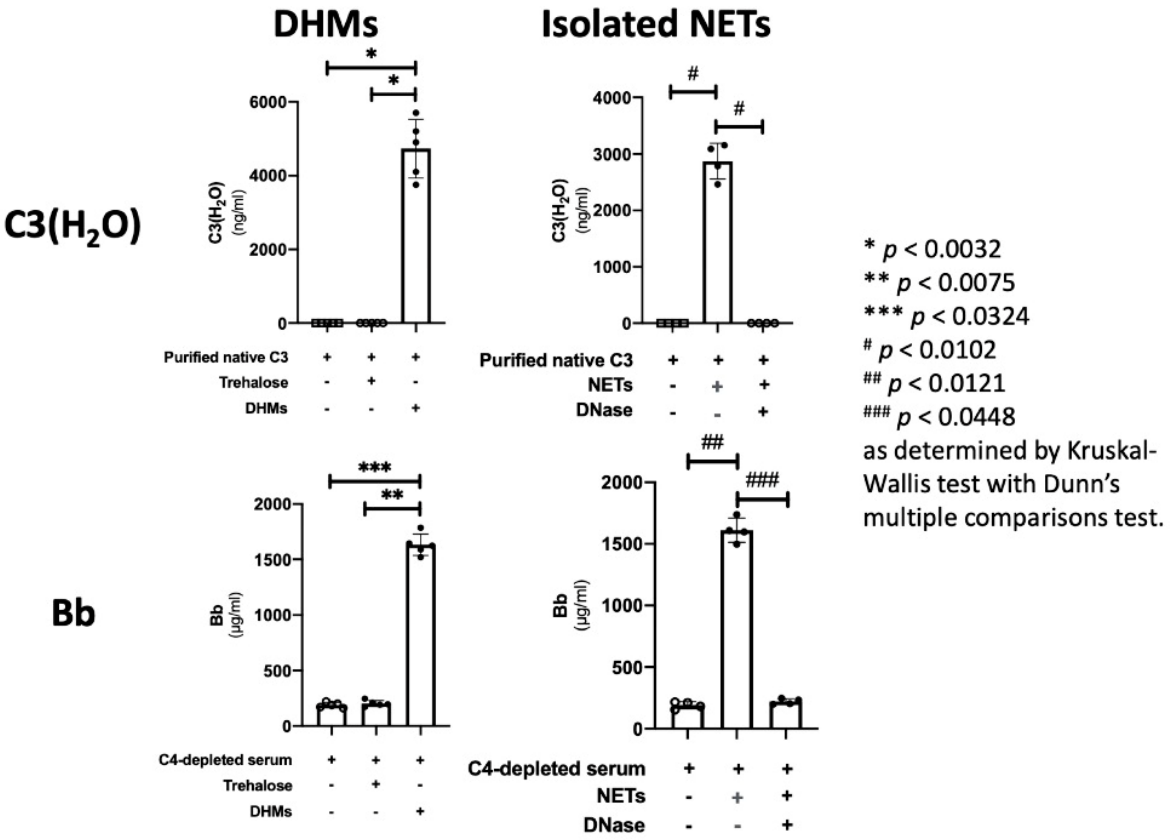
Sanjaya Sahu[1], Michelle Elvington[2], John Atkinson[1], Alfred Kim[1]
[1]Washington University School of Medicine, Medicine/rheumatoogy, St Louis, United States of America, [2]Kypha, Inc., St. Louis, United States of America

Background/Purpose: Systemic lupus erythematosus (SLE) relies on complement activation to drive many of the pathophysiologic features of this disease. We noted that patients with SLE have constitutive activation of the complement component C3 via the alternative pathway (1). The rate limiting step of alternative pathway activation is the conformational change of native C3 to C3(H_2O), a process that is termed tickover and thought to be a spontaneous process. Additionally, prior work has shown that stimulated neutrophils can drive C3 activation, which in turn further activates neutrophils, producing neutrophil extracellular traps (NETs) (2). As NETs are a key feature of SLE pathophysiology, and activated neutrophils can activate C3, we hypothesized that NETs promote alternative pathway activation in SLE by promoting the conformational change of native C3 to C3(H_2O).

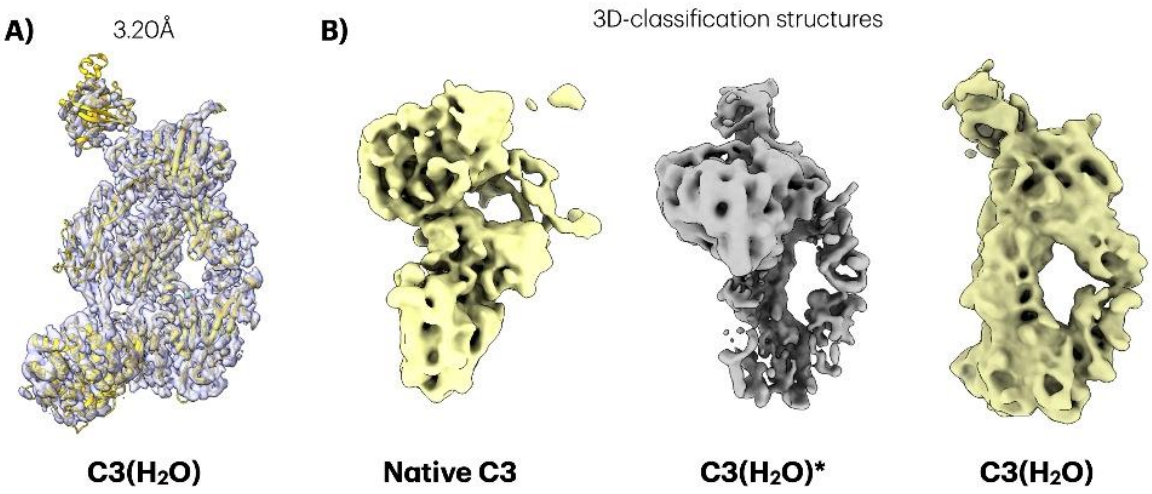
Methods: To independently assess whether NETs can activate C3, we leveraged a recently developed acellular mimic of NETs, DNA-histone mesostructures (DHMs), that possess the ultrastructural and functional properties of NETs (3). Purified human native C3 and C4-depleted human serum (Complement Technologies, Tyler, Tx, USA) were added to DHMs or DNA-histone-free DHMs (control). C3(H_2O) and factor Bb were assessed using ELISA. Isolated human neutrophils were obtained from consented healthy controls and activated by phorbol myristate acetate (PMA), some in the presence of DNAse to digest NETs. Images of neutrophils were obtained using a Zeiss LSM 880 Confocal with AiryScan. Cryo-electron microscopy (cryo-EM) was applied to elucidate the atomic structures of native C3 and C3(H_2O) using the Titan Krios G3 300kV Cryo-TEM. All processing of single-particle cryo-EM data was undertaken using cryoSPARK and RELION software.

Results: DHMs and isolated NETs from activated human neutrophils drove the rapid (< 5 minutes) and nearly complete (>90%) activation of native C3 into C3(H_2O) with the formation of a product of alternative pathway activation Bb, suggesting a contact-mediated mechanism is sufficient to activate the alternative pathway (Fig 1). AiryScan

confocal fluorescence microscopy confirmed the colocalization of native C3 with DHMs or NETs.



The first atomic-level structural determination of C3(H_2O) has been resolved to 3.20 angstrom (Fig 2A). Additionally, while native C3 that has been freeze-thawed once to create a mixture of native C3 and C3(H_2O) revealed a structural intermediate that likely represents a metastable conformation termed C3(H_2O)* that native C3 adopts as it converts to C3(H_2O) (Fig 2B).



Conclusions: We found that NETs are sufficient to activate the alternative pathway of complement through the likely contact-mediated conversion of native C3 to C3(H_2O). Given the high NET load and elevated serum iC3b levels (supporting alternative pathway activation) in SLE, we suspect that this may be the etiology for constitutive C3 activation observed in patients in SLE. We also generated the first atomic-level structural determination of C3(H_2O) using cryo-EM, along with identification of a structural intermediate between native C3 to C3(H_2O). These structures can be leveraged to identify small molecules that can interfere with alternative pathway activation, which may represent novel therapeutics in SLE and other alternative pathway-mediated diseases. References: 1. Kim et al, Arthritis Rheumatol, 2019, doi: 10.1002/art.40747 2. Camous et al, Blood, 2011, doi: 10.1182/blood-2010-05-283564 3. Weerappuli et al, Adv Healthc Mater, 2019, doi: 10.1002/adhm.201900926

O023a / #736

Topic: *AS07 - Cutaneous Lupus*
Late-Breaking Abstract

ABSTRACT CONCURRENT SESSION 03: INNATE AND ADAPTIVE IMMUNITY IN SLE
22-05-2025 1:40 PM - 2:40 PM

CELLULAR AND MOLECULAR IMMUNOPROFILING OF LUPUS PANNICULITIS: ELUCIDATING THE ROLES OF CYTOTOXIC T CELLS, B CELLS, AND COMPLEMENT ACTIVATION

Milad Ameri, Marie-Charlotte Brüggen
University of Zurich, Dermatology, Zürich, Switzerland

Background/Purpose: Lupus panniculitis (LP) is a rare manifestation of cutaneous lupus erythematosus characterized by chronic inflammation of subcutaneous white adipose tissue (SWAT). Despite its distinct clinical and histopathological features, the pathomechanisms driving LP remain poorly understood, leading to untargeted therapeutic strategies. This study aimed to elucidate the cellular and molecular mechanisms underlying LP using imaging mass cytometry (IMC) and NanoString nCounter technology to identify immune signatures and gene expression profiles associated with the disease.

Methods: Biopsies from eight LP patients and six healthy controls (HC) were analyzed. Cell populations and spatial interactions were assessed via IMC, while gene expression profiles were evaluated using NanoString.

Results: LP lesions demonstrated extensive leukocyte infiltration, predominantly comprising T cells (CD2+) (48%), B cells (CD20+) (14%), and macrophages (15%). T cells exhibited a cytotoxic (CD8+, Granzyme B+) and skin-homing (CLA+) phenotype, with Th1 polarization driven by type II interferon signaling. B cells displayed strong spatial interactions with naïve T cells. Antigen-presenting cells (APCs) such as dendritic cells and M1 macrophages were abundant and engaged in close interactions with cytotoxic T cells. Abundance of immune cells, particularly B cells, T cells, and cytotoxic cells, in LP was confirmed at mRNA level. LP exhibited significant activation of adaptive immune pathways, with upregulation of T and B cell signaling genes (CD3D, CD8A, CD19) and antigen presentation pathways (MHC Class I and II). A Th1-dominant profile, driven by interferon signaling (STAT1, IRF7) and cytotoxic pathways (TRAIL, TNFRSF1B). Innate immunity in LP showed significant upregulation of Toll-like receptor (TLR) signaling genes (TLR1, TLR2, MYD88). Immunometabolism pathways were altered, with upregulation of IDO1, a key enzyme in tryptophan metabolism, while AHR was downregulated. Complement pathways were activated with upregulation of classical components (**C1QA**, **C1QB**) and other regulatory changes.

Conclusions: This study highlights the role of cytotoxic and skin homing T- and B-cell-predominated immune response and complement activation and immunometabolic dysregulation is involved in LP. The findings provide valuable insights into cellular interactions and gene expression profiles, suggesting potential therapeutic targets, including interferon inhibitors, complement regulators, and metabolic modulators, to improve LP management.

O024 / #733

Topic: *AS24 - SLE-Treatment*
Late-Breaking Abstract

ABSTRACT CONCURRENT SESSION 04: ADVANCING LUPUS THERAPIES AND INSIGHTS
22-05-2025 1:40 PM - 2:40 PM

ENDOTHELIAL BRD4 PARTICIPATES IN THE DEVELOPMENT OF LUPUS NEPHRITIS

Xuan Wang[1], Weiru Zhang[2], Xin Ni[3]
[1]General practice, and National International Joint Research Center for Medical Metabolomics, Xiangya Hospital, Central South University, Changsha, China, [2]General practice, Xiangya Hospital, Central South University, Changsha, China, [3]National International Joint Research Center for Medical Metabolomics, Xiangya Hospital, Central South University, Changsha, China

Background/Purpose: Lupus nephritis (LN) is a common and lethal immune-related kidney disease, in which the pathological basis is vasculitis. The core of the LN is the interaction between immune-endothelial cells, but its molecular regulatory mechanism, especially in endothelial, is not clear. BRD4, a member of the BET protein family, is a histone reader that regulates inflammation and proliferation. Previous studies have found that JQ1, a BRD4 inhibitor, can partially relieve the progression of LN in mice, but the mechanism of BRD4 in LN is not clear.

Methods: We initially utilized the single-cell transcriptome of the kidney from lupus MRL/lpr mice to investigate the predominant cell types and BRD4 expression levels. These findings were subsequently validated in kidney tissues from both lupus patients and mouse models through flow cytometry and immunohistochemistry. Then, female MRL/lpr mice were treated with endothelial specific knockout virus of BRD4 ($BRD4^{\Delta EC}$-shRNA-AAV) by tail vein injection at the age of 8 weeks. Two model of LN (MRL/lpr and R848 induced mice) were used to test whether new BRD4 inhibitor NWHD870 has a therapeutical effect in vivo. Finally, human glomerular renal endothelial (HRGEC) were transfected with BRD4 overexpression and stimulated with interferon, RNA-seq, Co-IP and CHIP-seq were used to explore key transcription factors that interact with BRD4 in endothelial cells.

Results: First, We identified that renal endothelial cells serve as the primary functional cells in the kidney tissue of lupus mice, and observed a significant upregulation of BRD4 expression in ECs in both lupus patients and mouse models. Then, compared with the virus control group, $BRD4^{\Delta EC}$-shRNA-AAV injection significantly improved the kidney injury (proteinuria, glomerular basement membrane thickening and IgG deposition, renal mitochondrial abnormalities, tertiary lymphoid structures formation and CD3 + T

cell infiltration) of MRL/lpr mice, and ameliorated the lymph node proliferation, serum antibody production, and inflammatory damage of heart and skin. Next, we also treated MRL/lpr mice and R848-induced lupus mice with novel BRD4 inhibitor NHWD870, and found that it had a similar significant therapeutic effect on lupus kidney injury. Furthermore, in HRGEC with BRD4 overexpression, we performed RNA-seq and verified that the pro-inflammatory factors CXCL10, CXCL8 and endothelial damage indicators PECAM1 are significantly increased, and the endothelial cells were performed with a high degree of permeability and inflammatory cell (T cell and Mac) adhesion. Immune-ralated signaling pathway, leukocyte transendothelial transport and glomerulonephritis signaling pathway were enriched. After simulation of IFN, we further found that BRD4 overexpression significantly aggravates IFN-induced endothelial damage, while BRD4 inhibition significantly improves endothelial damage. Finally, in HRGEC, we further find Fli-1 was a key transcription factor binding as well as interaction with BRD4. Overexpression of Fli-1 results in endothelial damage aggravation, while inhibition of Fli-1 improves endothelial damage. BRD4 interacts with Fli-1 in the nucleus and forms a transcription complex evidenced by phase separation in HRGEC. BRD4-Fli-1 transcription complex acts as an enhancer, which regulates the expression of CXCL10, CXCL8 and PECAM1, leading to the progression of LN.

Conclusions: This study reveals that the high expression of BRD4 in renal endothelial cells is associated with LN, and its molecular mechanism may involve the activation of BRD4-Fli-1 transcription complex, the promotion of the expression of CXCL10, CXCL8 and PECAM1 in renal endothelial cells, and the infiltration of T cells in the kidney. Therefore, BRD4 is a potential therapeutic target for LN.

O025 / #750

Topic: *AS15 - Lupus Nephritis-Clinical*
Late-Breaking Abstract

ABSTRACT CONCURRENT SESSION 04: ADVANCING LUPUS THERAPIES AND INSIGHTS
22-05-2025 1:40 PM - 2:40 PM

RESULTS FROM THE REGENCY TRIAL ASSESSING EFFICACY AND SAFETY OF OBINUTUZUMAB IN ACTIVE LUPUS NEPHRITIS

Brad Rovin[1], Richard Furie[2], Jay Garg[3], Mittermayer Santiago[4], Gustavo Aroca-Martínez[5], Adolfina Zuta Santillán[6], Harini Raghu[3], Imran Hassan[7], Bongin Yoo[3], Elsa Martins[8], Himanshi Sehgal[8], Theodore Omachi[3], Thomas Schindler[8], William Pendergraft Iii[3], Ana Malvar[9]
[1]The Ohio State University College of Medicine, Department Of Internal Medicine, Columbus, United States of America, [2]Northwell Health, Division Of Rheumatology, Great Neck, United States of America, [3]Genentech, Inc., South San Francisco, United States of America, [4]Federal University of Bahia, Bahiana School of Medicine and Public Health and UFBA, and Clínica SER da Bahia, Salvador, Brazil, [5]Universidad Simón Bolívar and Colombia y Clínica de la Costa, Barranquilla, Colombia, [6]Instituto de Ginecología y Reproducción, Lima, Peru, [7]Hoffmann-La Roche Ltd, Mississauga, Canada, [8]F. Hoffmann-La Roche Ltd, Basel, Switzerland, [9]Organización Médica de Investigación, Buenos Aires, Argentina

Background/Purpose: Obinutuzumab, a humanized type II anti-CD20 monoclonal antibody, is approved for B-cell malignancies. In the Phase II NOBILITY trial of patients with active lupus nephritis (LN; NCT02550652), study participants receiving obinutuzumab in addition to standard therapy were significantly more likely to achieve complete renal response than those receiving placebo in addition to standard therapy. The results of the Phase III REGENCY trial (NCT04221477), performed to verify NOBILITY, are presented here.

Methods: REGENCY, a Phase III, double-blind placebo-controlled trial, randomized adults with biopsy-proven active proliferative LN 1:1 to placebo or one of two intravenous obinutuzumab dosing schedules (1000 mg: Day 1, Weeks 2, 24, 26, ±50 and 52) in addition to standard therapy. The primary endpoint was complete renal response (CRR, defined as urine protein-to-creatinine ratio [UPCR] <0.5 g/g, estimated glomerular filtration rate [eGFR] ≥85% of baseline and no intercurrent events of rescue therapy, treatment failure, death or early study withdrawal) at Week 76 and assessed in the intention-to-treat population. Key secondary endpoints included CRR at Week 76 with successful prednisone taper to ≤7.5 mg/day between Weeks 64 and 76, and UPCR <0.8 g/g at Week 76 with no intercurrent events, change in eGFR from baseline to Week 76

and renal-related events or death through Week 76. Incidence and severity of adverse events through Week 76 were compiled.

Results: Of 271 patients randomized, 135 were randomized to obinutuzumab and 136 to placebo. At Week 76, 46.4% of patients in the obinutuzumab group and 33.1% in the placebo group achieved CRR (adjusted difference, 13.4%; 95% CI, 2.0% to 24.8%; *P*=0.0232). More patients in the obinutuzumab group achieved CRR at Week 76 with successful prednisone taper (42.7% vs 30.9%, adjusted difference, 11.9%; 95% CI, 0.6% to 23.2%; *P*=0.0421) and a proteinuric response (UPCR <0.8 g/g) with no intercurrent events at Week 76 (55.5% vs 41.9%; adjusted difference, 13.7%; 95% CI, 2.0% to 25.4%; *P*=0.0227). Numerical changes in eGFR from baseline to Week 76 favored obinutuzumab compared with placebo, and fewer patients in the obinutuzumab group experienced the composite outcome of death or renal-related events through Week 76. Pre-specified subgroup analyses demonstrated numerically greater CRR rates with obinutuzumab in patients with potentially more active disease at enrollment, such as those with class IV LN, concomitant class V disease, baseline UPCR ≥3 g/g or greater baseline serologic activity. No new safety signals were observed based on the established safety profile of obinutuzumab in oncology indications. More coronavirus disease 2019 (COVID-19) events were observed in the obinutuzumab group, which primarily occurred during the acute phase of the COVID-19 pandemic. There were 3 deaths in the obinutuzumab group and 1 in the placebo group, which were mainly complications of COVID-19.

Conclusions: Obinutuzumab plus standard therapy was more effective than placebo plus standard therapy for achieving CRR, a clinically meaningful surrogate of kidney function, in patients with LN, while exhibiting an acceptable safety profile.

O026 / #740

Topic: *AS22 - SLE Heterogeneity*
Late-Breaking Abstract

ABSTRACT CONCURRENT SESSION 04: ADVANCING LUPUS THERAPIES AND INSIGHTS
22-05-2025 1:40 PM - 2:40 PM

MULTI-OMIC INTEGRATION REVEALS THREE MOLECULAR SUBTYPES WITH DISTINCT IMMUNOLOGICAL PHENOTYPES IN A COHORT OF 722 SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS

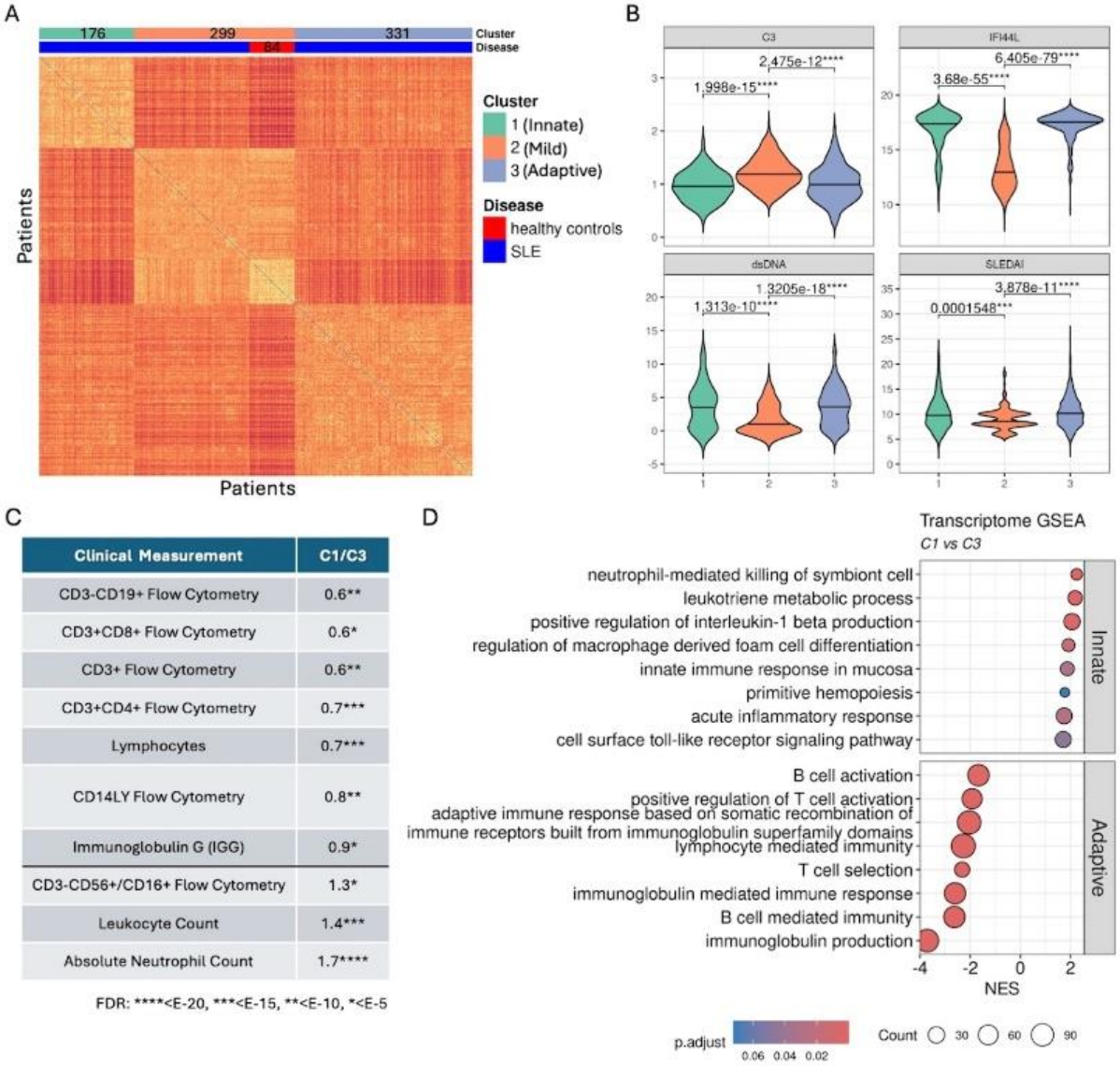
Helen Masson, David Gemperline, James Scherschel, Guilherme Rocha, Christoph Preuss, Javier Munoz Briones, Matthew Linnik, Richard Higgs, Ernst Dow
Eli Lilly, Indianapolis, United States of America

Background/Purpose: Integrative omics approaches offer a powerful strategy to dissect the complex biological networks and pathways involved in disease pathophysiology. However, integrating diverse data types with varying scales, biological contexts, and feature numbers poses significant challenges. This study aims to: i) identify molecular subtypes of SLE patients via a multi-omic integrative approach, ii) characterize these clusters using molecular and clinical data, and iii) identify the most discriminant subset of features for patient classification.

Methods: Similarity Network Fusion (SNF) was used to integrate baseline transcriptomic (RNAseq), proteomic (Olink), and epigenomic (EMseq) data from the whole blood of 722 SLE patients that were randomized to placebo plus standard of care in phase 3 clinical trials (NCT03616964, NCT03616912), and 84 healthy controls. Patient subgroups were identified via spectral clustering, and cluster robustness was determine using a bootstrapping approach (n = 30). Clusters were characterized with omics data via differential expression and gene set enrichment analysis (GSEA). Clusters were also characterized with clinical metrics via t-tests and random forest analysis. Finally, we utilized Data Integration Analysis for Biomarker Discovery using Latent cOmponents (DIABLO) modeling to identify potential biomarkers associated with these SLE classes.

Results: Integration of the omics datatypes identified three distinct clusters of individuals: cluster 1 (n = 176), cluster 2 (n = 299), and cluster 3 (n = 331). All 84 healthy controls were grouped within cluster 2 (Fig 1A). Notably, clustering based on individual datatypes failed to reproduce these distinct clusters. Clinical data revealed that SLE patients in cluster 2 exhibited significantly lower dsDNA, IFI44L, and SLEDAI scores, along with higher complement (C3) levels compared to the other clusters (Fig 1B), indicating a milder form of SLE. This is consistent with the fact that these SLE patients

clustered with the healthy controls. Additional clinical measurements (Fig 1C) and pathway enrichment analysis (Fig 1D) revealed distinct signatures in the other two clusters: cluster 3 displayed an elevated adaptive immunity signature, while cluster 1 was characterized by innate immunity signatures. Finally, integrating all three datatypes using the DIABLO modeling approach identified three latent components with a minimal set of discriminating biomarkers for each cluster.



Clinical Measurement	C1/C3
CD3-CD19+ Flow Cytometry	0.6**
CD3+CD8+ Flow Cytometry	0.6*
CD3+ Flow Cytometry	0.6**
CD3+CD4+ Flow Cytometry	0.7***
Lymphocytes	0.7***
CD14LY Flow Cytometry	0.8**
Immunoglobulin G (IGG)	0.9*
CD3-CD56+/CD16+ Flow Cytometry	1.3*
Leukocyte Count	1.4***
Absolute Neutrophil Count	1.7****

FDR: ****<E-20, ***<E-15, **<E-10, *<E-5

Figure 1. SLE patient clusters and characterization. **A)** Spectral clustering of patient-patient similarities calculated from the SNF-fused data. **B)** Distribution of conventional SLE metrics among the 3 SNF clusters (excluding healthy patients). Significant differences assessed with a t-test and false discover rate (FDR). **C)** Significant clinical differences between Cluster 1 and Cluster 3 using t-test and FDR. Fold change (C1/C3) greater than 1 indicates increased measurements in Custer 1 compared to Cluster 3. **D)** Normalized Enrichment Score (NES) of select GO terms from a GSEA analysis comparing C1 vs C3 using RNAseq. Positive NES indicates increased activity in C1, and vice-versa.

Conclusions: Multi-omic integration revealed three molecularly distinct clusters of SLE patients. Using orthogonal datatypes (clinical and omics), we characterized these clusters into three novel classifications: mild, innate-driven, and adaptive-driven immunity. This work helps our understanding of the complex heterogenous nature of SLE and will guide targeted treatment approaches with innate or adaptive involvement.

O027 / #730

Topic: *AS24 - SLE-Treatment*
Late-Breaking Abstract

ABSTRACT CONCURRENT SESSION 04: ADVANCING LUPUS THERAPIES AND INSIGHTS
22-05-2025 1:40 PM - 2:40 PM

CLINICAL IMPACT OF C-CAR168, A NOVEL ANTI-CD20/BCMA COMPOSITE AUTOLOGOUS CAR-T THERAPY, IN REFRACTORY LUPUS NEPHRITIS

Nan Shen[1], Huihua Ding[1], Wensi Li[2], Yiwei Shen[1], Chunyan Zhang[1], Yan Ye[1], Ran Wang[1], Shaoying Yang[1], Chunmei Wu[1], Dai Dai[1], Chengxiao Zheng[2], Yuan Qian[2], Xiaobing Luo[3], Thule Trinh[3], Judy Zhu[2], Jiaqi Huang[3], Yihong Yao[3]
[1]Ren Ji Hospital, Shanghai Jiao Tong University, School of Medicine, Department Of Rheumatolog, Shanghai, China, [2]Shanghai Abelzeta Ltd., Shanghai, China, [3]AbelZeta Inc., Rockville, United States of America

Background/Purpose: Despite advances in targeted therapies, refractory lupus nephritis (LN) represents a significant therapeutic challenge. C-CAR168 is a novel composite CAR-T cell therapy directed against CD20 and B cell maturation antigen (BCMA), that simultaneously targets mature B cells and plasma cells, both involved in lupus pathogenesis.[1] We report initial findings from seven patients with severe LN in this first-in-human study (NCT06249438).

Methods: This is a phase 1, open-label, dose-escalation and expansion study to evaluate the safety, efficacy and cellular kinetics of C-CAR168. For entry, patients must have biopsy-proven LN, increased 24h urinary protein (UP ≥ 1.0 g/24h) or urinary protein-to-creatinine ratio (UPCR) ≥ 1000 mg/g and have been exposed to ≥ 2 immunosuppressants (IS) and/or biologic agents. Eligible patients underwent steroid and IS tapering, leukapheresis, and lymphodepletion followed by a single infusion of C-CAR168. Clinical and laboratory features were monitored and CAR-T cell kinetics were assessed by quantitative PCR and flow cytometry.

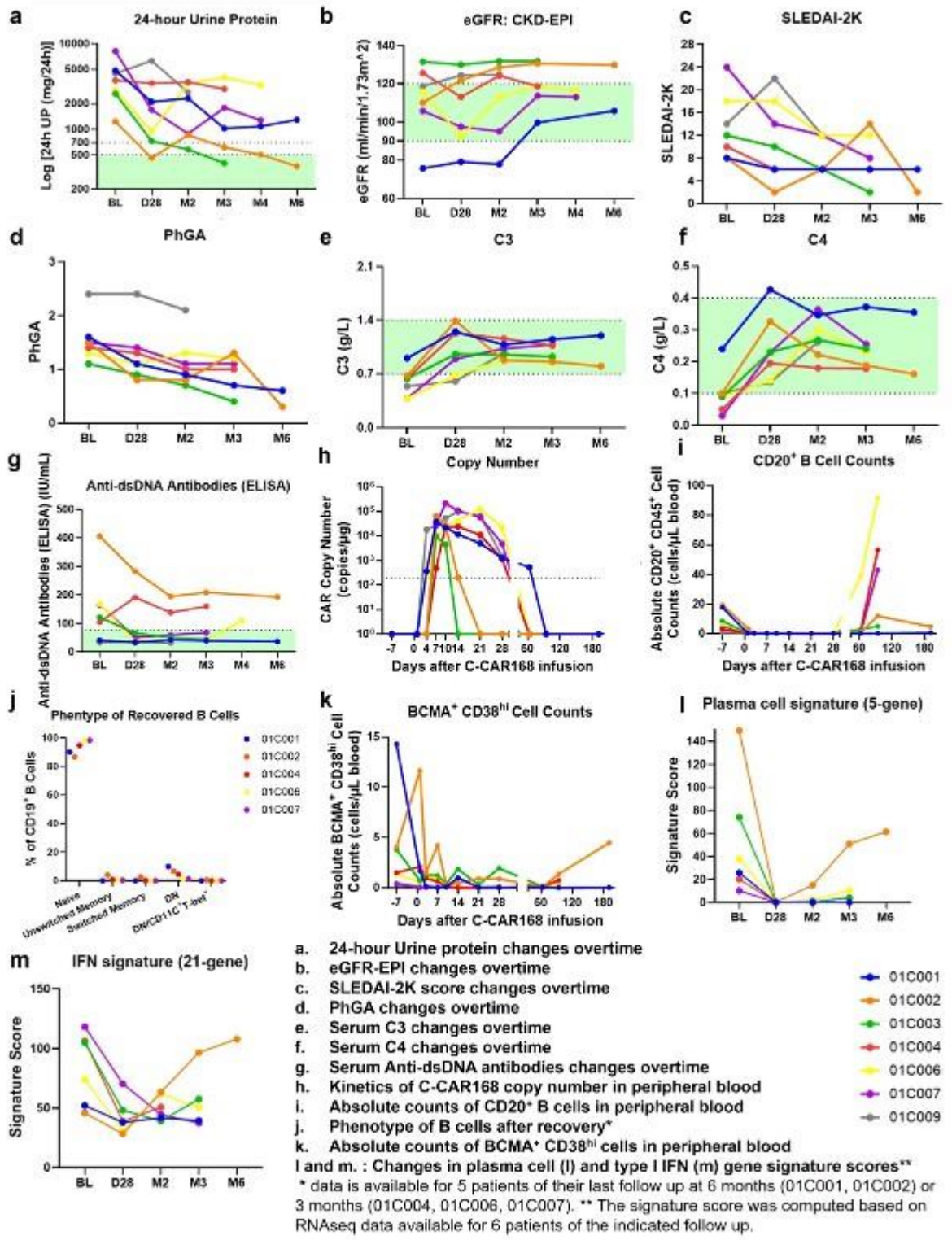
Results: As of January 14th, 2025, 7 patients with refractory LN received C-CAR168 therapy, with 4 dosed at 0.75×10^6 cells/kg and 3 at 1.5×10^6 cells/kg. The treated population had long-standing refractory disease (median SLE duration 9 years, LN 5 years) with exposure to a median of 4 IS or biologic agents. Renal histology showed predominantly mixed proliferative and membranous patterns. Active disease was evidenced by elevated proteinuria (UP range: 1227.2-8156.9mg/24h) and SLEDAI-2K scores (range: 8-24).[Table 1]

	Total N=7
Median Age (range), yr	30 (26-41)
Female, n (%)	6 (85.7)
Median SLE duration (range), yr	9 (5-14)
Median LN duration (range), yr	5 (2-9)
No of IS/biologic agents exposed (except steroids), n (range)	4 (3-8)
Previous treatment, n (%)	
Steroids	7 (100)
Hydroxychloroquine	6 (85.7)
Cyclophosphamide	6 (85.7)
Mycophenolate mofetil	6 (85.7)
Azathioprine	2 (28.6)
Tacrolimus	4 (57.1)
Leflunomide	3 (42.9)
Ciclosporin	1 (14.3)
Methotrexate	2 (28.6)
Iguratimod	4 (57.1)
Telitacicept	3 (42.9)
Belimumab	2 (28.6)
Rituximab	1 (14.3)
LN ISN/RPS, n (%)	
III+V	2 (28.6)
IV+V	3 (42.9)
III/IV+V	1 (14.3)
V	1 (14.3)
NPSLE history, n (%)	1 (14.3)
Baseline characteristics	
SLEDAI-2K, median (range)	12 (8-24)
PhGA, median (range)	1.5 (1.1-2.4)
ANA titer ≥ 1:80, n (%)	7 (100)
Anti-dsDNA Ab (Farr), median (range)	62.84 (13.5->100)
Low complement, n (%)	6 (85.7)
eGFR-CKD-EPI (ml/min×1.73m^2) , median (range)	115.91 (75.75-131.53)
24h UP (mg/24h) , median (range)	3713.7 (1227.2-8156.9)
UPCR (mg/g) , median (range)	2635.09 (1644.19-10841.93)

With median follow-up of 121 days, treatment-emergent adverse events included cytokine release syndrome in four patients (57.1%), all grade 1-2, with median onset at day 1 and resolution within 8 days. One patient experienced transient grade 3-4 thrombocytopenia (days 9-13) that was resolved with platelet transfusion. Notably, no immune effector cell-associated neurotoxicity syndrome, severe infections, or serious adverse events were observed. Clinical response was marked by successful withdrawal of all IS, with four patients (57.1%) also discontinuing steroids, whereas three continued on low dose prednisone (5-10 mg/d). The first two evaluable patients at 6 months achieved SLE Responder Index-4 and ≥ 50% reduction in proteinuria, with one also achieving Definition Of Remission In SLE (DORIS), Lupus Low Disease Activity State (LLDAS) and complete renal response. One patient with shorter follow-up showed early complete renal response at month 3. All patients maintained stable renal function

without deterioration in estimated glomerular filtration rate. Most patients demonstrated improvements in disease activity measures (SLEDAI-2K, PhGA) and serological improvements including complement normalization and reduction in anti-dsDNA antibodies.[Fig 1] C-CAR168 expanded in all patients along with a rapid and profound depletion of circulating CD20+ B cells and plasma cells. B cells recovered in 6/7 patients by month 2 with the majority of recovered B cells being naïve B cells. Substantial decreases of blood plasma cell and type 1 IFN gene signature scores[2,3] were observed post treatment.[Fig

1]



Conclusions: Initial results show promising efficacy and safety of C-CAR168 treatment in refractory LN, with reduced proteinuria, preserved renal function and improvement in laboratory and extra-renal features of LN, enabling withdrawal of IS. While the safety profile and early response signals are favorable, larger trials with longer follow-up are needed to validate the clinical impact of C-CAR168 in treatment of refractory

LN. **Reference:** [1] Huang J. et al., Arthritis Rheumatol. 2024; 76 (suppl 9). [2] Streicher K, et al., Arthritis Rheumatol. 2014 Jan;66(1):173-84. [3] Yao Y, et al., Hum Genomics Proteomics. 2009 Nov 17;2009:374312.

O028 / #834

Topic: ***AS12 - Genetics, Epigenetics, Transcriptomics***
Late-Breaking Abstract

ABSTRACT CONCURRENT SESSION 04: ADVANCING LUPUS THERAPIES AND INSIGHTS
22-05-2025 1:40 PM - 2:40 PM

TRANSCRIPTOME ANALYSIS OF QUIESCENT SLE CASES UNCOVERS DYSREGULATED PATHWAYS ASSOCIATED WITH DISEASE FLARES

Lorenzo Beretta[1], Guillermo Barturen[2], Torsten Witte[3], Ignasi Rodriguez Pintó[4], Ricard Cervera[5], Rafaela Ortega-Castro[6], Falk Hiepe[7], László Kovacs[8], Bohácsi Virág[8], Raquel Faria[9], Barbara Vigone[1], Marta Alarcón-Riquelme[2], Ioannis Parodis[10]
[1]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Referral Center For Systemic Autoimmune Diseases, Milan, Italy, [2]Centre for Genomics and Oncological Resea, University Of Granada, Granada, Spain, [3]Hannover Medical School, Hannover, Germany, Hannover, Germany, [4]Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunye, Department of Autoimmune Diseases, Barcelona, Spain, [5]Hospital Clinic de Barcelona. IDIBAPS. University of Barcelona, Autoimmune Diseases, Barcelona, Spain, [6]Servicio de Reumatología, Hospital Universitario Reina Sofía, Cordoba, Spain, [7]Charité Universitätsmedizin, Berlin, Germany, [8]University of Szeged, Department Of Rheumatology And Immunology, Faculty Of Medicine, Szeged, Hungary, [9]Unidade Local de Saude Santo António, Unidade De Imunologia Clínica, Porto, Portugal, [10]Karolinska Institutet, Department Of Medicine, Solna, Stockholm, Sweden

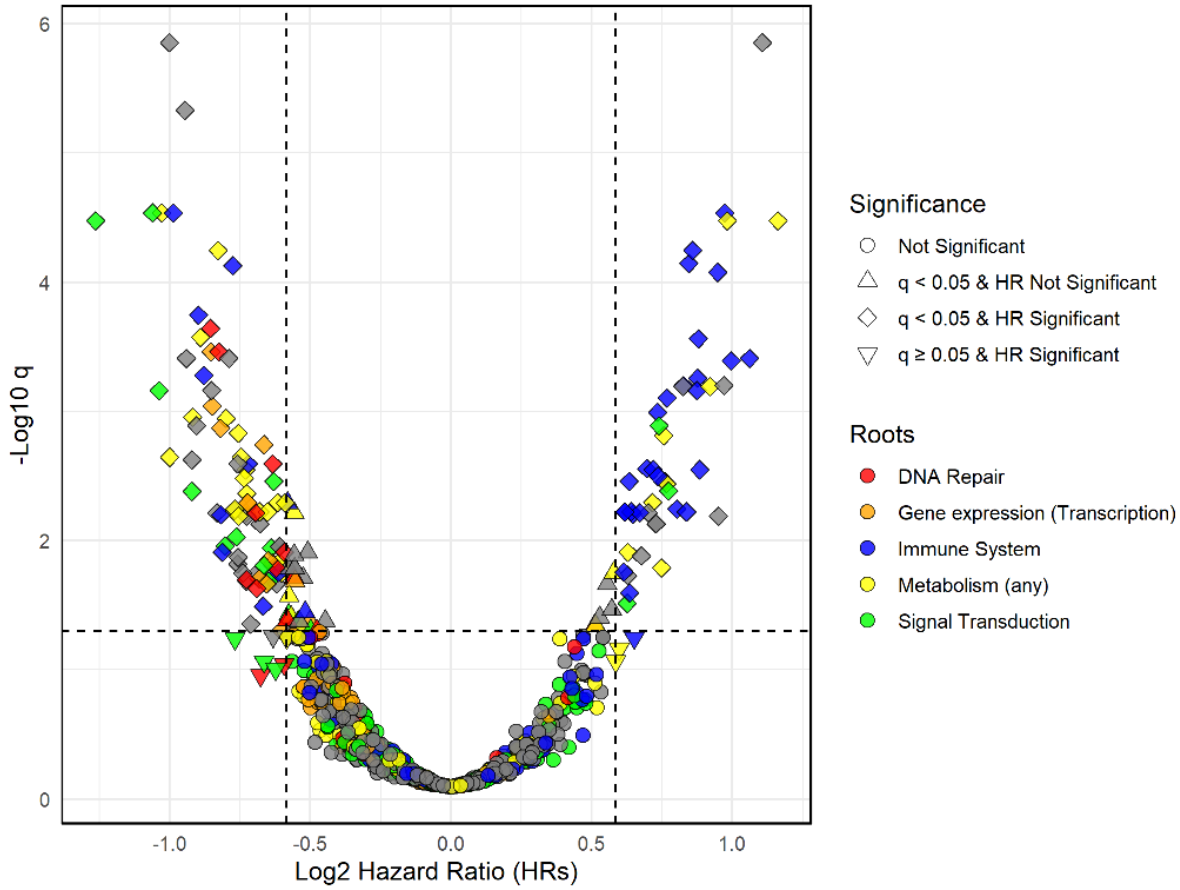
Background/Purpose: Unpredictability is a major challenge in systemic lupus erythematosus (SLE). Routinely used clinical and laboratory parameters fail to predict the risk of and time to flare, or the type of flare that a patient might develop. We hypothesise that molecular biosignatures may better predict flaring and might thus have merit in disease monitoring.

Methods: Eligible for this analysis were SLE patients from the European multicenter PRECISESADS project (NCT02890121) with available transcriptome data and long-term follow-up including registration of disease flares. The analysis was restricted to patients with quiescent disease at the time of sampling, defined as a clinical SLEDAI-2K score <6. Flare was defined as any increase in disease activity resulting in a change of therapy. For each patients individualized Reactome pathways according to the Functional Analysis of Individual Microarray Expression (FAIME) algorithm, were calculated. Time-dependent analysis for interval censored data was conducted with parametric models correcting for relevant confounding covariates associated with flares and individual regression weights. Results were deemed significant if they yielded false-discovery rate

q value <0.05 and a hazard ratio (HR) >1.5 for causative pathways or <0.667 for protective ones.

Results: Long-term data were available in 131 patients, including 85 with a clinical SLEDAI-2K <6 at baseline. At the time of blood sampling, those patients had a mean (SD) age of 47.5 (13.9) years and a mean disease duration of 15.7 (9.7) years, and they were mostly women (n=84, 98.8%). The mean clinical SLEDAI-2K was 1.5 (1.5) and the mean total SLEDAI-2K was 3.6 (2.3). At baseline, 59 (69.4%) patients were treated with hydroxychloroquine, 25 (29%) with synthetic immunosuppressants, and 36 (42.3%) with glucocorticoids at a mean daily dose of 2.3 (0.5) mg of a prednisone equivalent. After a mean observation time of 6.9 (2.6) years, flares had occurred in 30 patients (35%). Among those 30 patients, the first flare was developed after a mean time of 3.0 (2.0) years, and the non-cumulative count of those flares per domain was 18 articular, 9 cutaneous, 5 constitutional, 4 haematological, 3 vascular, and 2 renal flares. Overall, 1265 Reactome pathways were explored, of those 131 were significant according to the applied selection criteria; 83 and 48 pathways were associated with increased or reduced flaring hazards, respectively (Figure 1). Flaring patients had a reduced capability of repairing damaged DNA (especially pyrimidines), increased DNA damage due to impaired telomere function, an increased activity interferon-related pathways, an increased activity of the complement system, an increased inflammasome, reduced CTLA4 and CD28 inhibitory mechanisms, a disrupted circadian clock as well as several metabolic alterations.

Conclusions: Our findings reveal that specific pathway deregulations linked to SLE pathogenesis may herald the occurrence of flares in quiescent patients. Impaired DNA repair, increased interferon signaling, complement activation, inflammasome upregulation, and reduced CTLA4/CD28 inhibitory mechanisms suggest a predisposition to immune dysregulation preceding clinical flares. These insights highlight potential molecular predictors of flaring and suggest that targeted immunomodulation or specific interventions may be warranted in selected patients to prevent flares and mitigate the risk of long-term damage accrual, ultimately improving disease monitoring and personalized therapeutic strategies in SLE.


6
4
2
0
-Log10 q
-1.0
-0.5
0.0
0.5
1.0
Log2 Hazard Ratio (HRs)
Significance
Not Significant
q < 0.05 & HR Not Significant
q < 0.05 & HR Significant
q ≥ 0.05 & HR Significant
Roots
DNA Repair
Gene expression (Transcription)
Immune System
Metabolism (any)
Signal Transduction

O029 / #396

Topic: ***AS24 - SLE-Treatment***

ABSTRACT CONCURRENT SESSION 04: ADVANCING LUPUS THERAPIES AND INSIGHTS
22-05-2025 1:40 PM - 2:40 PM

RESET SLE: CLINICAL TRIAL EVALUATING CABA-201, A FULLY HUMAN, AUTOLOGOUS 4-1BB ANTI-CD19 CAR T CELL THERAPY IN NON-RENAL SLE AND LUPUS NEPHRITIS

Saira Sheikh[1], Vimal Derebail[1], Natalie Grovner[1], Gaurav Gulati[2], Mehrdad Abedi[2], Jonathan Hogan[3], Yvonne White[3], Carl Dicasoli[3], Rebecca Estremera[3], Jenell Volkov[3], Daniel Nunez[3], Jason Standanlick[3], Mallorie Werner[3], Justin Cicarelli[3], Quynh Lam[3], Thomas Furmanak[3], Fatemeh Nezhad[3], Samik Basu[3], Raj Tummala[3], David Chang[3]
[1]UNC, Chapel Hill, United States of America, [2]UC Davis, Sacramento, United States of America, [3]Cabaletta Bio, Philadelphia, United States of America

Background/Purpose: The goal of current therapies for systemic lupus erythematosus (SLE) is to control disease activity, reduce organ damage, and decrease long-term morbidity and mortality. Therapies providing durable clinical responses without requiring chronic immunosuppressive drugs are lacking. CD19-targeting chimeric antigen receptor (CAR) T cells have achieved durable drug-free responses in SLE participants in an academic program. CABA-201 is a fully human, autologous 4-1BB anti-CD19-CAR T cell therapy, designed to deeply and transiently deplete CD19 positive cells following a one-time infusion. This approach may enable an “immune system reset” with the potential for durable response without chronic immunosuppression. RESET-SLE™ (NCT06121297) is an ongoing Phase 1/2 trial evaluating safety and efficacy of CABA-201 in 2 independent SLE cohorts of non-renal SLE and lupus nephritis (LN).

Methods: Eligible participants are ≥18 to ≤65 years with SLE, ANA+ or anti-dsDNA+, and SLEDAI 2K ≥8 despite standard of care (SOC) therapy (non-renal cohort) or active, biopsy-confirmed class III or IV ± V LN despite SOC (LN cohort). A single infusion of $1x10^6$ CAR T cells/kg is administered following a preconditioning regimen (fludarabine 25 mg/m^2/d on Days -5, -4 and -3, and cyclophosphamide1,000 mg/m^2 on Day -3). All non-corticosteroid immunosuppressive and antimalarial agents are stopped by preconditioning. Participants require a minimum of 4 days in participant monitoring post-CABA-201 infusion. The primary endpoint is safety and tolerability within 28 days of infusion. Secondary endpoints include translational assessments (including CAR T cell pharmacokinetics and impact on peripheral B-cell populations) and efficacy outcomes (including SLEDAI-2K, SRI and renal responses).

Results: As of 23 October 2024, 4 participants have been dosed with CABA-201 in the RESET-SLE™ trial, 3 participants in the non-renal SLE cohort and 1 participant with Class III nephritis in the LN cohort (Table 1).

Table1: Baseline characteristics of CABA-201 treated participants

	RESET-SLE™			
Patient / Cohort	**SLE1**	**SLE2**	**SLE3**	**LN1**
Age, sex	26 M	36 F	44 F	24 F
Disease duration	~6 years	~17 years	~9 years	~2 years
Autoantibodies	dsDNA	dsDNA	dsDNA	dsDNA
Baseline Disease activity*	**SLEDAI-2K**			
	26	10	8	22
	UPCR (mg/dL)			
	1.08†	n/a	n/a	7.22
Therapies at screening	GC, MMF, HCQ	GC, AZA, HCQ	HCQ, MMF, BEL	GC, ANI, VOC, MMF, HCQ
Other prior therapies	CYC, BEL, VOC, TAC	MSC, RTX, ANI, BEL, ADA, MTX	GC, MTX	BEL, LEF
GC Dose at Screening (mg/day)#	10	7	n/a	20

Footnotes: *Baseline disease activity = activity before pre-conditioning; †SLE1 had Class V Lupus Nephritis; inclusion criteria for LN cohort requires class III/IV LN; #Prednisone equivalent. ANI, anifrolumab; AZA, azathioprine; BEL, belimumab; ; CYC, cyclophosphamide; dsDNA, double-stranded DNA; GC, glucocorticoid; HCQ, hydroxychloroquine; LEF, leflunomide; MSC, Mesenchymal Stem Cells; MMF, mycophenolate mofetil; MTX, methotrexate; RTX, rituximab; SLEDAI, SLE disease activity index; UPCR, urinary protein-to-creatinine ratio; VOC, voclosporin.

CABA-201 has been well-tolerated with Grade 1 cytokine release syndrome (CRS) (fever) reported in 2 participants. The LN participant also experienced Grade 4 immune effector cell-associated neurotoxicity syndrome (ICANS), which resolved rapidly and completely following standard management. This participant had recent fevers and very active, refractory disease (SLEDAI-2K =22 at baseline despite being on 5 systemic treatments for SLE), including hospitalization for pericardial effusion 18 days prior to infusion and aseptic fever 4 days prior to infusion. Subsequently, the protocol was revised to include a delay of at least 2 weeks from any febrile event or infection prior to CABA-201 infusion and the use of anti-seizure prophylaxis (as reported in previous academic data) in all participants. Early clinical response has been observed in all 4 treated participants. Each participant remains off all SLE-related immunosuppression with 2 completing a steroid taper. Translational data from 3 of the first 4 participants show that expansion of CABA-201 peaked between day(D) 15 and D29 post-infusion, with the LN participant also having a 2nd peak at D29, followed by rapid contraction. Peripheral B cells were rapidly reduced with nadir occurring D22 post-infusion. B cells with a translational naive phenotype were detected at 2 months post infusion in the first 2 participants to date.

Conclusions: Data from SLE participants dosed with CABA-201 show CAR T cell expansion, peripheral B cell depletion, CRS grade and frequency and clinical response consistent with previously reported data. These initial data suggest the potential for CABA-201 to reset the immune system in SLE participants and allow participants to discontinue immunosuppressive therapies and taper corticosteroids while achieving compelling clinical responses.

O030 / #400

Topic: ***AS23 - SLE-Diagnosis, Manifestations, & Outcomes***

ABSTRACT CONCURRENT SESSION 05: EMERGING INSIGHTS ON THE MANAGEMENT OF LUPUS MANIFESTATIONS AND COMORBIDITIES
23-05-2025 1:40 PM - 2:40 PM

DIRECT AND INDIRECT COSTS ASSOCIATED WITH DAMAGE ACCRUAL: RESULTS FROM THE SYSTEMIC LUPUS INTERNATIONAL COLLABORATING CLINICS (SLICC) INCEPTION COHORT

Megan Barber[1], John Hanly[2], Murray Urowitz[3], Ian Bruce[4], Yvan St. Pierre[5], Caroline Gordon[6], Sang-Cheol Bae[7], Juanita Romero-Diaz[8], Jorge Sanchez-Guerrero[3], Sasha Bernatsky[5], Daniel J Wallace[9], David Isenberg[10], Anisur Rahman[10], Joan . Merrill[11], Paul R Fortin[12], Dafna D Gladman[3], Michelle Petri[13], Ellen Ginzler[14], Mary-Anne Dooley[15], Rosalind Ramsey-Goldman[16], Susan Manzi[17], Andreas Jönsen[18], Graciela S. Alarcón[19], Ronald Van Vollenhoven[20], Cynthia Aranow[21], Meggan Mackay[22], Guillermo Ruiz-Irastorza[23], S. Sam Lim[24], Murat Inanc[25], Kenneth Kalunian[26], Soren Jacobsen[27], Christine Peschken[28], Diane L Kamen[29], Anca Askanase[30], Ann Clarke[1]
[1]University of Calgary, Division Of Rheumatology, Cumming School Of Medicine, Calgary, Canada, [2]Dalhousie University, Halifax, Canada, [3]University of Toronto, Toronto, Canada, [4]Centre for Musculoskeletal Research, Division of Musculoskeletal and Dermatological Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, United Kingdom, [5]Research Institute of the McGill University Health Center, Montreal, Canada, [6]University of Birmingham, Birmingham, United Kingdom, [7]Hanyang University Hospital for Rheumatic Diseases,, Seoul, Korea, Republic of, [8]The National Institute of Medical Sciences and Nutrition, Mexico City, Mexico, [9]Cedars-Sinai Medical Center, Los Angeles, United States of America, [10]University College London, London, United Kingdom, [11]Oklahoma Medical Research Foundation, Clinical Immunology Program, Oklahoma City, United States of America, [12]Universite Laval, Centre Arthrite - Chu De Québec, Quebec City, Canada, [13]John Hopkins University School of Medicine, Division of Rheumatology, Baltimore, United States of America, [14]SUNY Downstate Medical Center, New York, United States of America, [15]University of North Carolina at Chapel Hill, Chapel Hill, United States of America, [16]Northwestern University, Chicago, United States of America, [17]Allegheny Singer Research Institute, Allegheny Health Network, Pittsburgh, United States of America, [18]Lund University Faculty of Medicine, Lund, Sweden, [19]Marnix E. Heersink School of Medicine, Rheumatology, Birmingham, United States of America, [20]Amsterdam University Medical Centers, Department Of Rheumatology And Clinical Immunology, Amsterdam, Netherlands, [21]Feinstein Institute for Medical Research, Manhasset, United States of America, [22]Feinstein Institutes for Medical Research, Northwell Health, New York, United States of America, [23]Biobizkaia Health

Research Institute, Bilbao, Spain, [24]Emory University, Division Of Rheumatology, Atlanta, United States of America, [25]Istanbul University, Istanbul, Turkey, [26]University of California San Diego, San Diego, United States of America, [27]Copenhagen University Hospital Center for Rheumatology and Spine Diseases, Copenhagen, Denmark, [28]University of Manitoba, Winnipeg, Canada, [29]Medical University of South Carolina, Charleston, United States of America, [30]Columbia University Medical Center, New York, United States of America

Background/Purpose: We described the direct healthcare costs associated with damage accrual in patients in the Systemic Lupus International Collaborating Clinics (SLICC) Inception Cohort [1]. However, our estimates only included partial direct costs and indirect costs from lost productivity were not included. We supplemented our primary data by querying a cohort subset on all healthcare use and lost time in paid/unpaid labour and provide estimates of complete direct and indirect costs for the full cohort, stratified by damage.

Methods: Between 1999 and 2011, SLE patients from 31 centres in 10 countries were enrolled into the SLICC Inception Cohort within 15 months of diagnosis and data on disease damage (SLICC/ACR Damage Index [SDI]) and limited healthcare use (i.e., hospitalizations, medications, and dialysis) were collected annually through to July 2022. Starting in 2015, 18 sites collected supplemental economic data annually (i.e., visits to physicians, non-physician healthcare professionals, and the emergency room, laboratory tests, radiological/other diagnostic procedures, outpatient surgeries, help obtaining medical care, and lost time in paid/unpaid labour). Direct costs were calculated by multiplying each health resource by its corresponding 2023 Canadian unit cost. Total indirect costs included: 1) absenteeism (time lost from paid labour because of illness), 2) presenteeism (degree of patient self-reported productivity impairment in paid/unpaid labour, based on a visual analogue scale), and 3) opportunity costs (additional time patients would be working in paid/unpaid labour if not ill). Opportunity costs were calculated as the difference between the time patients reported working versus that worked by an age, sex, and geographic-matched general population in paid/unpaid labour. Indirect costs from paid/unpaid labour were valued using age-and-sex-specific wages from Statistics Canada. Multiple imputation was used to predict missing cost values for the patients in the full cohort who provided only utilization data for hospitalizations, medications, and dialysis for all observations. At each assessment, patients were assigned to one of six damage states (i.e., SDI = 0, 1, 2, 3, 4, >= 5) and annual costs, both unimputed and including imputations, were stratified by SDI score. Means and 95% confidence intervals were computed and compared.

Results: 1694 patients (88.8% female, 48.9% White, mean age at diagnosis 34.6 years, mean disease duration at cohort enrolment 0.5 years), were followed for a mean of 10.5 (SD 5.3) years. Of these 1694 patients, 766 (89.7% female, 41.4% White, mean age at

diagnosis 33.0 years, mean disease duration at cohort enrolment 0.4 years) completed the supplemental economic questionnaire. Their mean disease duration at the time of introduction of the supplemental questionnaire was 10.9 (range 3.9-19.5) years and this cohort subset provided this additional economic data for a mean of 3.5 (SD 1.9) years. Among the cohort subset completing the supplemental economic questionnaire, on average, indirect costs, primarily from unpaid labour, accounted for 81.1% of total costs (Table 1). For the full cohort, annual direct and indirect costs increased with increasing SDI (SDI=0: total costs $33,812 [95%CI $31,088, $36,537]; SDI >=5: total costs $90,839 [95%CI $82,275, $99,403]) (Table 2).

Table 1. Annual complete direct, indirect, and total costs (in 2023 Canadian dollars) for the cohort subset providing complete cost data, stratified by SDI (n = 2414 observations). Values are means.

SDI	0	1	2	3	4	>= 5
Patients, n	369	187	142	82	47	48
Observations, n (%)	1098 (45.5)	502 (20.8)	351 (14.5)	213 (8.8)	126 (5.2)	124 (5.1)
Direct Costs	**5481**	**5762**	**6611**	**14451**	**12944**	**29822**
Hospital stays	843	1110	1253	1747	2243	4491
Medications	2086	1910	2535	2710	2686	2142
Physicians	924	1010	971	1391	1606	1663
Tests	616	804	931	874	772	1394
Dialysis	0	0	0	6334	3797	18597
Other*	1012	949	922	1394	1840	1535
Indirect Costs	**25316**	**38932**	**39551**	**45320**	**53280**	**52418**
Paid labour	**5626**	**10132**	**12145**	**17577**	**22054**	**21396**
Absenteeism	1251	1235	1227	1848	1957	1832
Presenteeism	6270	6627	7419	4953	5308	4658
Opportunity	-1895	2270	3500	10777	14780	14907
Unpaid labour	**19689**	**28800**	**27406**	**27743**	**31226**	**31021**
Presenteeism	10362	10524	10842	12384	9469	10873
Opportunity	9328	18277	16564	15359	21757	20148
Total Costs	**30797**	**44714**	**46162**	**59771**	**66225**	**82240**

*Other includes non-physician healthcare professional, emergency room visits, outpatient surgeries, and help obtaining medical care

Table 2. Annual imputed complete direct, indirect, and total costs (in 2023 Canadian dollars) for the full cohort, stratified by SDI (n = 15,106 observations).

SDI	Patients, n	Observations, n (%)	Complete Direct Costs, Mean (95%CI)	Indirect Costs, Mean (95%CI)	Total Costs Mean (95% CI)
0	1236	8090 (53.6)	5386 (5010, 5761)	28427 (25816, 31038)	33812 (31088, 36537)
1	674	3028 (20.0)	6493 (6042, 6945)	37411 (34338, 40483)	43904 (40778, 47030)
2	410	1866 (12.4)	7781 (7038, 8523)	40003 (36455, 43550)	47783 (44004, 51563)
3	267	1118 (7.4)	12650 (11234, 14067)	47035 (43595, 50476)	59686 (55842, 63529)
4	134	480 (3.2)	16167 (13739, 18595)	51786 (45604, 57968)	67952 (61041, 74864)
>=5	117	524 (3.5)	32020 (28330, 35709)	58819 (51342, 66297)	90839 (82275, 99403)

Conclusions: Patients with the highest versus the lowest SDIs incurred complete direct costs that were 5.9-fold higher and indirect costs 2.1-fold higher. However, patients with no or minimal damage still experienced considerably reduced productivity. Indirect costs exceeded direct, on average, by 4.5-fold, underscoring the importance of incorporating lost productivity in estimating the economic burden of SLE. **References** [1.] Barber MRW. Arthritis Care Res 2020;72:1800-1808.

O031 / #611

Topic: ***AS23 - SLE-Diagnosis, Manifestations, & Outcomes***

ABSTRACT CONCURRENT SESSION 05: EMERGING INSIGHTS ON THE MANAGEMENT OF LUPUS MANIFESTATIONS AND COMORBIDITIES
23-05-2025 1:40 PM - 2:40 PM

CHARACTERIZING ARTHRITIS SUBTYPES IN SLE: PREVALENCE, CLINICAL FEATURES, AND THE ROLE OF TYPE I INTERFERON SIGNATURES

Pankti Mehta, Fadi Kharouf, Virginia Carrizo Abarza, Qixuan Li, Laura Whittall-Garcia, Dafna D Gladman, Zahi Touma
University of Toronto Lupus Clinic, Division of Rheumatology, Schroeder Arthritis Institute, Krembil Research Institute, University Health Network, Toronto, Canada

Background/Purpose: Musculoskeletal involvement in Systemic Lupus Erythematosus (SLE) is one of the most prominent manifestations of the disease, featuring in both the classification criteria and disease activity assessments. It is presently unclear if specific subtypes of lupus arthritis—nondeforming nonerosive (NDNE), Jaccoud's arthropathy (JA), and rhupus, are associated with specific clinical associations. We aimed to study the prevalence of subtypes of lupus arthritis and determine their association with clinical features, serology, and type I interferon signature.

Methods: This is an observational cohort study of patients with arthritis (defined by the ACR or EULAR/ACR SLE classification criteria at presentation and SLEDAI 2K over follow-up) identified from a single-center SLE database (July 1970-Aug 2024) from both inception and prevalent cohorts. Demographic, clinical, laboratory (including interferon signature), radiographic features, and treatment variables were retrieved from the database. Descriptive statistics were used to outline features across three subtypes of arthritis; non-deforming arthritis (determined by clinical examination), arthritis with reducible deformities or JA, and arthritis with non-reducible deformities or rhupus. In the inception cohort, time to deformities was studied using cumulative incidence survival analysis. Factors associated with deforming arthritis were determined using multivariate Fine and Gray modelling as a time-to-event analysis for the inception cohort using age, sex, smoking, adjusted mean SLEDAI-2K, autoantibodies, complements, antimalarial, glucocorticoid, and immunosuppression use.

Results: Arthritis was observed in 1,248 of 2264 (55.12%) patients. 908 (72.6%) had non-deforming and 340 (27.2%) had deforming arthritis– 239 (19.2%) had JA, 101 (8.1%) had rhupus. The median age at diagnosis of SLE was comparable, though a higher proportion of females was observed in JA (p=0.03). The distribution of organ involvement and antibodies was similar across the three subtypes, except nervous system involvement (p=0.03) and anti-Ro antibodies (p=0.04) being more frequent in

rhupus. There was a trend toward higher mean SLEDAI-2K scores in JA (p=0.07), and the modified SDI (excluding musculoskeletal component) was the highest in rhupus (p<0.01). The distribution of rheumatoid factor and anti-citrullinated protein antibody positivity did not differ significantly across the three groups. The proportion of patients with high interferon signature was the greatest in JA, followed by non-deforming arthritis, and lastly, rhupus (p<0.01). Radiographs (n, 95) revealed erosive disease in 10 of 43 (23.2%) with JA, 12 of 36 (33.3%) with rhupus, and 2 of 16 (12.5%) with non-deforming arthritis. The use of glucocorticoids, mycophenolate mofetil, belimumab, and other biologics was most prevalent in JA, while methotrexate was higher in rhupus. (Table 1) In the inception cohort, the cumulative incidence plot showed a shorter time to the development of JA of 2.07 [1.00, 15.76] as compared to 4.64 [1.00, 9.78] years for rhupus. In the multivariate analysis, JA was associated with a higher adjusted mean SLEDAI 2K [1.09(1.01-1.19)] and female sex [3.3(1.14-12.5)]. No significant associations were observed with rhupus.

Table 1: Baseline demographic, clinical, laboratory, and treatment characteristics of patients with arthritis (n=1248)

Median (IQR)/n(%)	Non-deforming arthritis (n, 908)	Rhupus (n, 101)	Jaccoud's arthropathy (n, 239)	p-value**
Age at diagnosis	27.86 (20.56-38.27)	31.96 (22.37-40.40)	28.57 (21.60-38.68)	0.152
Sex, Female	798 (88.1)	92 (90.2)	225 (94.1)	**0.03**
Organ involvement ever				
Skin	813 (89.6)	97 (95.1)	217 (90.8)	0.2
Nervous system	316 (34.8)	48 (47.1)	94 (39.3)	**0.03**
Vasculitis	254 (28)	32 (31.4)	69 (28.9)	0.76
Renal	443 (48.8)	49 (48)	126 (52.7)	0.54
Serosal	170 (18.7)	19 (18.6)	52 (21.8)	0.57
Hematologic	680 (75)	76 (74.5)	186 (77.8)	0.64
Constitutional	296 (32.6)	42 (41.2)	87 (36.2)	0.16
Serology	812 (89.5)	93 (91.2)	221 (92.5)	0.37
Adjusted mean SLEDAI-2K	3.82 (2.3-5.9)	3.1 (2.1-5.2)	4.0 (2.6-6.1)	0.07
SDI#	0.00 (0.00, 1.00)	0.87 (0.00, 1.66)	0.50 (0.00, 1.24)	**<0.01**
Antibodies & complements				
Anti-Smith	376 (41.5)	41 (40.2)	110 (46)	0.41
Anti-RNP	446 (49.2)	55 (53.9)	134 (56.1)	0.14
Anti-Ro	513 (56.5)	71 (68.6)	135 (56.5)	**0.04**
Anti-La	290 (32.0)	35 (34.3)	77 (32.2)	0.90
Anti-Ribosomal P	77 (8.5)	10 (9.8)	213 (89.1)	0.50
Anti-Cardiolipin	288 (31.8)	39 (38.2)	77 (32.2)	0.41
Anti-dsDNA	686 (75.6)	81 (79.4)	193 (80.8)	0.20
Low C3	684 (75.4)	77 (75.5)	178 (74.5)	0.9
Low C4	444 (49)	40 (39.2)	110 (46)	0.15
Rheumatoid factor	145 (16.2)	18 (17.8)	38 (16.3)	0.1
Anti-CCP (130 patients)	10 (12.9)	5 (29.4)	3 (8.3)	0.11
High Interferon signature (318 patients)	122 (55.7)	7 (26.9)	49 (67.1)	**<0.01**
Treatment received ever				
Glucocorticoids	756 (85.3)	90 (88.2)	224 (94.9)	**<0.01**
Prednisone dose	10 (6.19-15)	9.1 (6.1-13.2)	10 (7.1-12.7)	0.5
Antimalarials	769 (86.8)	88 (86.3)	209 (88.6)	0.75
Mycophenolate Mofetil	254 (28.7)	31 (30.4)	92 (39)	**0.01**
Azathioprine	369 (41.6)	47 (46.1)	118 (50)	0.06
Methotrexate	195 (22)	41 (41.2)	72 (30.5)	**<0.01**
Cyclophosphamide	75 (8.5)	12 (11.8)	13 (5.5)	0.13
Rituximab	36 (4.1)	7 (6.9)	8 (3.4)	0.33
Belimumab	36 (4.1)	5 (4.9)	19 (8.1)	**0.04**

SDI: modified by excluding the musculoskeletal domain, *C- Complement, CCP- Citrullinated cyclic peptide, dsDNA- double-stranded Deoxyribo Nucleic Acid, SLEDAI- Systemic Lupus erythematosus Disease Activity Index, SLICC- Systemic Lupus erythematosus International Collaborating Clinics, DI- Damage Index, ** Chi-Square/ANOVA test across the three groups

Conclusions: Arthritis was observed in half the cohort, with the majority being non-deforming (72.6%). Among deforming arthritis, JA (19%) was more common than rhupus (8%). JA was associated with a high interferon signature, high disease activity, female sex, and a shorter time to development as compared to rhupus. These sheds light on two different mechanisms for deforming arthritis, with JA associated with SLE disease burden in contrast to rhupus. Erosions were observed in both types of deforming arthritis, blurring the line of radiologic differences historically outlined between them.

O032 / #273

Topic: ***AS23 - SLE-Diagnosis, Manifestations, & Outcomes***

ABSTRACT CONCURRENT SESSION 05: EMERGING INSIGHTS ON THE MANAGEMENT OF LUPUS MANIFESTATIONS AND COMORBIDITIES
23-05-2025 1:40 PM - 2:40 PM

MACHINE LEARNING CAN IDENTIFY AN ANTINUCLEAR ANTIBODY PATTERN THAT MAY RULE OUT SYSTEMIC AUTOIMMUNE RHEUMATIC DISEASES

Farbod Moghaddam[1], Javad Sajadi[1], Ann Clarke[1], Sasha Bernatsky[2], Karen Costenbader[3], Murray Urowitz[4], John Hanly[5], Caroline Gordon[6], Sang-Cheol Bae[7], Juanita Romero-Diaz[8], Jorge Sanchez-Guerrero[9], Daniel J Wallace[10], David Isenberg[11], Anisur Rahman[12], Joan . Merrill[13], Paul R Fortin[14], Dafna D Gladman[4], Ian Bruce[15], Michelle Petri[16], Ellen Ginzler[17], Mary-Anne Dooley[18], Rosalind Ramsey-Goldman[19], Susan Manzi[20], Andreas Jönsen[21], Graciela S. Alarcón[22], Ronald Van Vollenhoven[23], Cynthia Aranow[24], Meggan Mackay[25], Guillermo Ruiz-Irastorza[26], S. Sam Lim[27], Murat Inanc[28], Kenneth Kalunian[29], Soren Jacobsen[30], Christine Peschken[31], Diane L Kamen[32], Anca Askanase[33], Marvin Fritzler[1], Mina Aminghafari[1], May Choi[1]
[1]University of Calgary, Calgary, Canada, [2]McGill University, Medicine, Montreal, Canada, [3]Brigham and Women's Hospital, Rheumatology, Boston, United States of America, [4]University of Toronto, Toronto, Canada, [5]Dalhousie University, Halifax, Canada, [6]University of Birmingham, Birmingham, United Kingdom, [7]Hanyang University Hospital for Rheumatic Diseases,, Seoul, Korea, Republic of, [8]The National Institute of Medical Sciences and Nutrition, Mexico City, Mexico, [9]Krembil Research Institute, Toronto, Canada, [10]Cedars-Sinai Medical Center, Los Angeles, United States of America, [11]Department of Ageing, Rheumatology and Regenerative Medicine, Division of Medicine, University College London, London, United Kingdom, [12]University College London, London, United Kingdom, [13]Oklahoma Medical Research Foundation, Clinical Immunology Program, Oklahoma City, United States of America, [14]Universite Laval, Quebec City, Canada, [15]Queen's University Belfast, Belfast, United Kingdom, [16]John Hopkins University, Baltimore, United States of America, [17]SUNY Downstate Medical Center, New York, United States of America, [18]University of North Carolina at Chapel Hill, Chapel Hill, United States of America, [19]Northwestern University, Chicago, United States of America, [20]Allegheny Singer Research Institute, Allegheny Health Network, Pittsburgh, United States of America, [21]Lund University Faculty of Medicine, Lund, Sweden, [22]The University of Alabama at Birmingham, Rheumatology, Oakland, United States of America, [23]Amsterdam University Medical Centers, Department Of Rheumatology And Clinical Immunology, Amsterdam, Netherlands, [24]Feinstein Institute for Medical Research, Manhasset, United States of America, [25]Feinstein Institutes for Medical Research, Northwell Health, New York, United States of America, [26]Biobizkaia Health Research Institute, Bilbao, Spain, [27]Emory University, Division Of Rheumatology,

Atlanta, United States of America, [28]Istanbul University, Istanbul, Turkey, [29]University of California San Diego, San Diego, United States of America, [30]Copenhagen University Hospital Center for Rheumatology and Spine Diseases, Copenhagen, Denmark, [31]University of Manitoba, Winnipeg, Canada, [32]Medical University of South Carolina, Charleston, United States of America, [33]Columbia University Medical Center, New York, United States of America

Background/Purpose: Antinuclear antibody (ANA) testing is used to screen for systemic autoimmune rheumatic diseases (SARD) like systemic lupus erythematosus. It is well established that a nuclear dense fine-speckled (DFS) ANA pattern (AC-2), being rare among SARD patients, decreases the likelihood of these conditions. However, the AC-2 pattern is challenging for lab technologists to accurately identify due to similarities with other patterns, i.e., AC-4 (speckled) and AC-30 (nuclear speckled with mitotic plate staining), which *are* associated with SARDs. We determined if machine learning could accurately differentiate between AC-2 and SARD-related AC-4/AC-30 patterns.

Methods: 13,671 ANA images from SLE patients enrolled in the Systemic Lupus International Collaborating Clinics Inception Cohort (SLICC, n=2,825 images), non-SLE subjects enrolled in the Ontario Health Study (OHS, n=10,639 images), and the International Consensus on ANA Patterns (ICAP, n=207 images) were analyzed. All SLICC and OHS ANA were performed in one central laboratory using IFA on HEp-2 cells (NovaLite, Werfen, SD) and read on a digital IFA microscope (NovaView, Werfen, SD). A lab technologist (HH) with >30 years of experience identified AC-2, AC-4, and AC-30 images. Images were resized to 224x224 pixels. Three machine learning models (ANA Reader©) using a convolutional neural network (CNN) and an image feature extractor were developed to differentiate AC-2 from the other patterns. We also merged the outputs of all three CNNs to create a combined ANA Reader© model. 80% of the images were used for training and 20% for validation. We compared the performance of the four machine learning models (lab technologist as the reference standard) to determine the best prediction model.

Results: The lab technologist identified 308 AC-2, 957 AC-4, and 379 AC-30 images. All four models performed similarly with high area-under-the-curve (AUC) scores ranging from 96.5%-97.1% (Table 1). When comparing other performance metrics, the combined ANA Reader© model performed the best with the highest accuracy (93.0%), precision (92.7%), specificity (93.2%), and F1 score (92.7%). It was tied with another CNN model (Model 2) for the second most sensitive model (92.7%).

Table 1. Comparison of different ANA Reader© convolutional neural network (CNN) models and a combined model to differentiate

between AC-2 vs. AC-4 and AC-30 antinuclear antibody (ANA) patterns.						
CNN Model	**Accuracy (%)**	**Precision (%)**	**Sens (%)**	**Spec (%)**	**F1 (%)**	**AUC (%)**
1	89.5	90.6	87.3	91.5	88.9	96.7
2	90.4	87.9	92.7	88.1	90.3	96.5
3	84.2	76.1	98.2	71.2	85.7	97.1
Combined	93.0	92.7	92.7	93.2	92.7	96.6
Abbreviations: AUC, area-under-the-curve; CNN, convolutional neural network; Sens, sensitivity; Spec, specificity.						

Conclusions: We developed a highly precise and accurate machine learning model, ANA Reader©, that discriminates the nuclear DFS pattern (AC-2) from other similar ANA patterns, potentially speeding up the differentiation of those at risk vs. not at risk of SARDs and reducing the need for unnecessary rheumatologic investigations or assessments. External validation of our model in other cohorts will be done before this model is adopted into laboratories and clinical practice.

O033 / #701

Topic: ***AS23 - SLE-Diagnosis, Manifestations, & Outcomes***

ABSTRACT CONCURRENT SESSION 05: EMERGING INSIGHTS ON THE MANAGEMENT OF LUPUS MANIFESTATIONS AND COMORBIDITIES
23-05-2025 1:40 PM - 2:40 PM

10-YEAR ATHEROSCLEROTIC PLAQUE PROGRESSION AND INCIDENT CARDIOVASCULAR EVENTS IN SYSTEMIC LUPUS ERYTHEMATOSUS: THE IMPACT OF PERSISTENT CARDIOVASCULAR RISK FACTOR TARGET ATTAINMENT AND SUSTAINED DORIS REMISSION

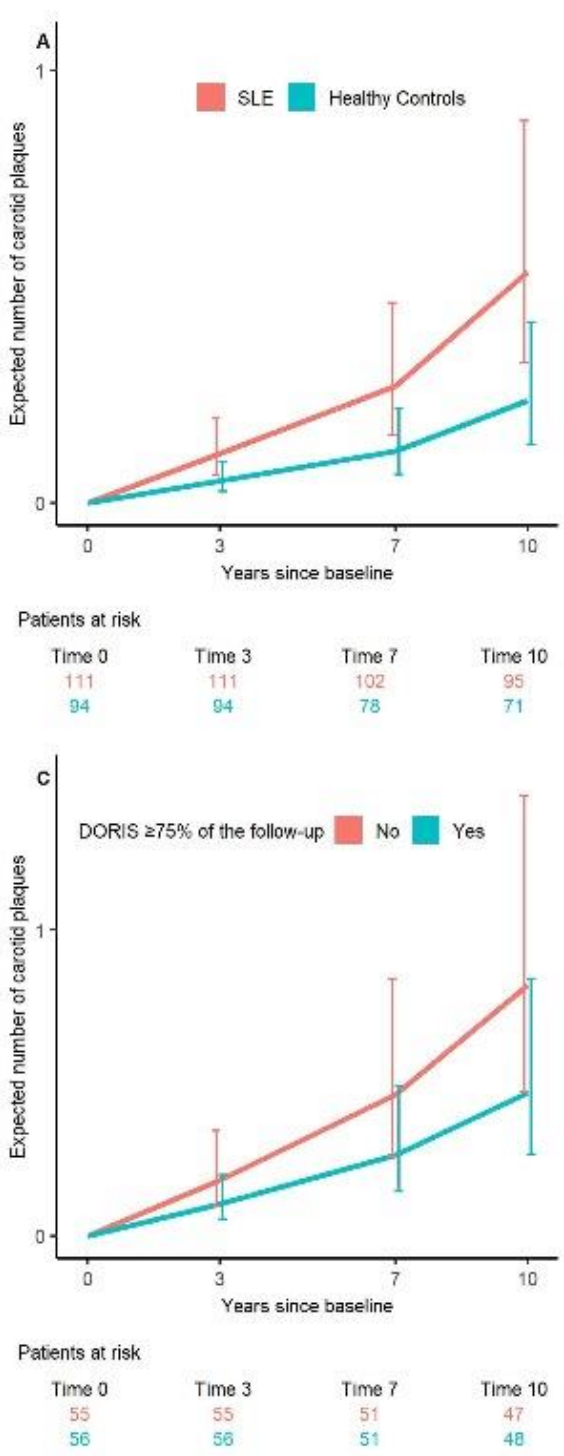
Nikolaos Papazoglou, Petros Sfikakis, Maria Tektonidou
National and Kapodistrian University of Athens, Joint Academic Rheumatology Program, Rheumatology Unit, First Department Of Propaedeutic Internal Medicine, “laiko” General Hospital, Medical School, Athens, Greece

Background/Purpose: Cardiovascular disease (CVD) is a leading cause of morbidity and mortality in Systemic Lupus Erythematosus (SLE). The role of sustained cardiovascular risk factor (CVRF) control and minimal disease activity on clinical and subclinical atherosclerosis remains underexplored in SLE. We assessed the impact of persistent traditional CVRF target attainment and sustained minimal disease activity on atherosclerotic plaque progression and incident cardiovascular events in patients with SLE over a 10-year follow-up period.

Methods: We prospectively analyzed 738 carotid ultrasound measurements (413 in SLE patients and 325 in age/sex-matched healthy controls [HC]) to assess new plaque development from baseline to 3-, 7-, and 10-year follow-up assessments. Multivariate mixed effects Poisson regression models examined potential predictors of plaque progression, including patient demographic characteristics, Systemic Coronary Risk Evaluation (SCORE), SCORE2, traditional cardiovascular risk factor (CVRF) target attainment as per the 2016 European Society of Cardiology guidelines, sustained achievement of Lupus Low Disease Activity State (LLDAS) and Definition of Remission in SLE (DORIS) clinical remission, cumulative glucocorticoid exposure, consistent hydroxychloroquine use, CVD-related medications, and persistent triple antiphospholipid antibody (aPL) positivity during the 10-year follow-up period. We assessed 10-year incident CVD events in SLE versus HC, and univariate Cox regression analysis examined potential associations. We evaluated the efficacy of carotid ultrasound in predicting CVD risk in the SLE cohort, comparing its performance to SCORE and SCORE2 alone.

Results: Patients with SLE had a 2.3-fold higher 10-year risk of carotid plaque progression than HC (Incidence Rate Ratio [IRR]: 2.26, 95% CI 1.34-3.81, p = 0.002)

(Table 1, model A). The expected 10-year evolution of the number of carotid plaques was higher in SLE versus HC (Figure 1A). The risk of plaque progression in SLE patients was reduced by 32% (IRR: 0.68, 95% CI 0.53-0.89, p = 0.004) for each CVRF persistently on target during the 10-year follow-up, including blood pressure, lipids, smoking, body weight, and physical activity (Table 1, model B). DORIS achievement ≥ 75% of the follow-up period was associated with a 43% decrease in atherosclerotic plaque progression risk (IRR: 0.57, 95% CI 0.34-0.95, p = 0.033) (Table 1, Model B). The expected 10-year evolution of the number of carotid plaques was lower in patients with more persistently attained CVRF targets during follow-up (Figure 1B), and in those achieving DORIS remission ≥ 75% of follow-up versus those who did not (Figure 1C). Ten-year risk of incident cardiovascular events was higher in SLE than HC individuals (eight versus one event, permutation-based log-rank p = 0.036), and was associated with persistent triple aPL positivity. The incorporation of carotid ultrasound in CVD risk assessment in SLE patients tripled our ability to predict the 10-year risk for CVD events from 12.5% to 37.5%.



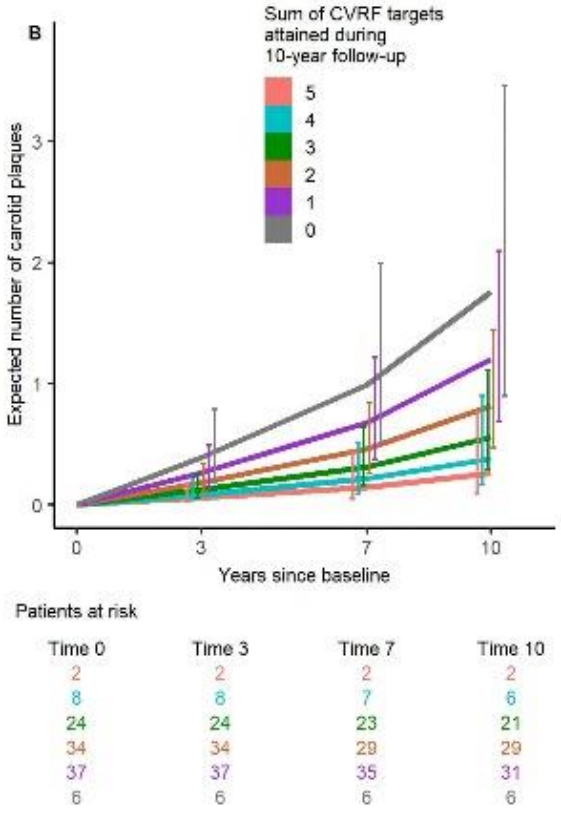


Figure 1. Expected 10-year evolution of the number of carotid plaques A) for typical SLE and healthy control (HCs), B) for typical SLE individuals with varying numbers of cardiovascular risk factor (CVRF) targets sustainedly attained, and C) for typical SLE individuals with versus without DORIS remission for ≥75% of follow-up

*A) Typical individuals are SLE patients or HCs with baseline characteristic values (included in multivariate model 4A of plaque progression in SLE versus HCs) set at the median for quantitative and at the mode for qualitative variables: no use of antihypertensives, lipid-lowering agents or antiplatelets, SCORE 0.1, eGFR 111 mL/min/1.73 m², no carotid plaques.

B) Typical SLE individuals are patients with baseline characteristic values (included in multivariate model 5A of plaque progression in SLE) set at the median for quantitative and at the mode for qualitative variables: 43 years old, no use of antihypertensives, lipid-lowering agents, or antiplatelets, no DORIS remission ≥75% of follow-up.

C) Typical SLE individuals are patients with baseline characteristic values (included in multivariate model 5A) set at the median for quantitative and at the mode for qualitative variables: 43 years old, no use of antihypertensives, lipid-lowering agents, or antiplatelets, and two CVRF targets sustainedly attained during the follow-up.

Table 1. Multivariate mixed effects Poisson regression models of carotid plaque progression in SLE versus healthy controls (model A), and within SLE (model B)

	IRR	95% CI	P value
Model A			
SLE versus healthy controls	2.26	1.34 - 3.81	**0.002**
Antihypertensives	1.02	0.61 - 1.71	0.938
Lipid-lowering agents	1.64	0.77 - 3.48	0.198
Antiplatelets	0.99	0.55 - 1.78	0.971
SCORE	1.16	0.96 - 1.42	0.132
eGFR	0.80	0.63 - 1.01	0.059
Number of carotid plaques	0.88	0.60 - 1.29	0.520
Model B			
Age (years)	1.03	(1.01, 1.06)	**0.010**
Antihypertensives	0.64	(0.37, 1.09)	0.100
Lipid-lowering agents	1.11	(0.50, 2.46)	0.800
Antiplatelets	0.89	(0.51, 1.55)	0.671
Sum of CVRF targets consistently attained throughout the follow-up period*	0.68	(0.53, 0.89)	**0.004**
DORIS75	0.57	(0.34, 0.95)	**0.033**

Variables refer to baseline assessment unless specified otherwise.
IRR: Incidence Rate Ratio; CI: confidence intervals; SCORE: Systemic Coronary Risk Evaluation prediction of 10-year fatal cardiovascular disease corresponding to the 2016 European Society of Cardiology (ESC) guidelines in low-risk countries; eGFR: estimated Glomerular Filtration Rate; CVRF: cardiovascular risk factor; DORIS75: maintaining Definition of Remission in SLE for at least 75% of the follow-up period.
*CVRF targets attained throughout the follow-up period represented targets consistently attained by the last follow-up assessment (3-, 7-, or 10-year) according to the 2016 ESC guidelines between blood pressure, Low-Density Lipoprotein (LDL), smoking, body weight (Body Mass Index and waist circumference), and physical activity
All models are also adjusted for the timepoints of carotid ultrasound measurements (as a qualitative covariate).

Conclusions: Patients with SLE experience a 2.3-fold higher 10-year atherosclerosis progression risk than HC, which is significantly mitigated by sustained CVRF control and prolonged clinical remission. Persistent triple aPL positivity is associated with increased incidence of CVD events in SLE. Carotid ultrasound may have an additive role in enhancing CVD risk assessment in patients with SLE.

O034 / #681

Topic: ***AS09 - Emerging Approaches in SLE Management***

ABSTRACT CONCURRENT SESSION 05: EMERGING INSIGHTS ON THE MANAGEMENT OF LUPUS MANIFESTATIONS AND COMORBIDITIES
23-05-2025 1:40 PM - 2:40 PM

FRAMEWORK FOR IMPLEMENTING TREAT-TO-TARGET IN SYSTEMIC LUPUS ERYTHEMATOSUS ROUTINE CLINICAL CARE: CONSENSUS STATEMENTS FROM AN INTERNATIONAL TASK FORCE.

Matteo Piga[1], Ioannis Parodis[2], Zahi Touma[3], Alexandra Legge[4], Manuel Francisco Ugarte-Gil[5], Ihsane Hmamouchi[6], José Gómez-Puerta[7], Hervé Devilliers[8], Margherita Zen[9], Jiacai Cho[10], Nelly Ziade[11], Johanna Mucke[12], Carlos Enrique Toro-Gutierrez[13], Shinji Izuka[14], Peter Korsten[15], Baïdy Sy Kane[16], Vera Golder[17], Benjamin Chong[18], Guillermo Pons-Estel[19], François Chasset[20], Laurent Arnaud[21]
[1]Università di Cagliari, Cagliari, Italy, [2]Karolinska Institutet, Department Of Medicine, Solna, Stockholm, Sweden, [3]Schroeder Arthritis Institute, Toronto Western Hospital, University of Toronto, Toronto, Canada, [4]Dalhousie University, Medicine, Halifax, Canada, [5]Hospital Guillermo Almenara Irigoyen. EsSalud., Rheumatology, Lima, Peru, [6]International University of Rabat, Health Sciences Research Centre (cress), Faculty Of Medicine,, Rabat, Morocco, [7]Rheumatology Department, Hospital Clínic, Universitat de Barcelona, Barcelona, Spain, BARCELONA, Spain, [8]Dijon university Hospital, Internal Medicine And Systemic Disease Unit And Cic-ec Inserm, Dijon, France, [9]University of Padua, Rheumatology Unit, Department Of Medicine, Padua, Italy, [10]National University Hospital, Division Of Rheumatology, Department Of Medicine,, Singapore, Singapore, [11]Saint Joseph University and Hotel Dieu de France Hospital, Rheumatology Department, Beirut, Lebanon, [12]Heinrich-Heine University, Department Of Rheumatology, Dusseldorf, Germany, [13]Pontificia Javeriana University,, Cali, Colombia, [14]The University of Tokyo, Department Of Allergy And Rheumatology, Graduate School Of Medicine, Tokyo, Japan, [15]St. Josef-Stift Sendenhorst, Department Of Rheumatology And Clinical Immunology, Sendenhorst, Germany, [16]Cheikh Anta DIOP University, Department Of Internal Medicine, Dakar, Senegal, [17]Monash Health, Melbourne, Australia, [18]University of Texas Southwestern, Dallas, United States of America, [19]Centro Regional de Enfermedades Autoinmunes y Reumáticas, Grupo Oroño, Rosario, Argentina, rosario, Argentina, rosario, Argentina, [20]Tenon's Hospital, Paris, France, [21]Department of Rheumatology, National Reference Center for Autoimmune Diseases (RESO), University Hospitals Strasbourg, Strasbourg, France

Background/Purpose: The adoption of Treat-to-Target (T2T) in routine clinical care for systemic lupus erythematosus (SLE) is limited, with evidence showing ongoing overuse of glucocorticoids (GCs) and inadequate disease control in many patients. An

international task force convened to address the challenges and identify effective strategies for implementing T2T in adult SLE patients in real-life settings.

Methods: The T2T task force comprised a multidisciplinary panel of 22 physicians with extensive experience in SLE management and 3 lupus patient research partners. The panel's geographical distribution included 9 (40.9%) experts from Europe, 4 (16.5%) from Asia-Pacific, 3 (13.6%) from North America, 3 (13.6%) from Latin America, and 3 (13.6%) from Africa. Through a scoping review and online discussions, the panel mapped, identified, and discussed the current limitations and best available options for implementing T2T in SLE. Drawing from these findings, the panel formulated a series of potential framework statements, which were rigorously debated and refined before reaching an agreement through a Delphi consensus process.

Results: The resulting framework outlines 5 overarching principles and 11 specific statements (Table).

Overarching principles for practical implementation of T2T in SLE		Median (IQR)
A	The T2T strategy should be implemented as early as possible during the course of the disease, ideally starting as soon as the diagnosis of SLE is made.	10 (0)
B	The choice of treatments should follow the latest local / international recommendations.	10 (1)
C	Decisions regarding the implementation of the T2T strategy should be shared between the patient and the medical team (i.e., shared decision-making).	10 (0)
D	Non-pharmacological measures and patient education should be incorporated into the T2T strategy.	10 (0)
E	Telehealth and digitally-supported platforms can be used as additional tools to facilitate the implementation of T2T in SLE.	9 (2)
Consensus statements for implementing T2T in SLE routine clinical care		
#1	The main goal of the T2T strategy is to achieve remission as early as possible after diagnosis (or a flare), ideally reaching remission on treatment before M6 in non-renal SLE, and before M12 in lupus nephritis, and then to maintain remission for the longest possible duration.	10 (1)
#2	Remission ON treatment is defined by the absence of clinical disease activity AND a maximum dose of 5mg/day of prednisone-equivalent AND stable or decreasing doses of maintenance treatment, if any.	10 (1)
#3	If remission ON treatment is not achieved within the pre-specified timeframe: 1) therapeutic adherence should be assessed; and 2) treatments should be optimized.	10 (0)
#4	In case of active disease, we recommend follow-up visits every 1 to 3 months, based on the type and severity of organ-involvement.	10 (1)
#5	Once Remission ON treatment is achieved, we suggest follow-up visits every 3 to 6 months until prolonged remission is achieved.	9·5 (1)
#6	In case of a suspected flare, a medical consultation should be performed as soon as possible (if needed remotely), and treatment adjusted accordingly after assessing therapeutic adherence.	10 (0)
#7	Prolonged remission is defined as remission* lasting 5 years or more.	9 (3)
#8	Once prolonged remission is reached, we suggest follow-up visits every 3-6 months, based on previous organ involvements (e.g. lupus nephritis).	9 (2·75)
#9	Tapering of GCs should be considered at every visit.	10 (0)
#10	Discontinuation of GCs should be considered in patients in remission ON treatment.	10 (0)
#11	The possibility to taper and then discontinue DMARDs should be assessed in patients in prolonged remission who have previously discontinued GCs	10 (1)

**Remission ON or OFF treatment: As stated elsewhere, not all patients can discontinue GCs. The possibility of discontinuing GCs should be assessed at every visit.*

T2T: treat to target; SLE: Systemic Lupus Erythematosus; M6: Month 6; M12: Month 12; GCs: Glucocorticoids; DMARDs: Disease-modifying antirheumatic drugs.

The T2T strategy should be implemented as early as possible during the disease course, favored by a shared decision-making approach and by including non-pharmacological measures and telehealth in the process. The importance of achieving remission within a prespecified timeframe is highlighted. At the same time, LLDAS is highlighted as a valuable alternative target when remission cannot be achieved or maintained. The task force suggests time intervals between visits, guided by disease activity status. If

remission is not attained within the recommended timeframe, adherence to therapy should be evaluated, and treatment strategies should be optimized accordingly. At each clinical visit, prioritizing the tapering of glucocorticoids is essential, with complete discontinuation considered for patients in sustained remission, ideally by following a slow tapering protocol. Prolonged remission, defined as remission lasting five years or longer, opens the possibility of discontinuing immunosuppressants and/or biologics in patients who have successfully discontinued glucocorticoids. Goals, priorities, and areas of investigation for future research endeavors were identified (Figure).

Conclusions: Although formal evidence proving the superiority of T2T to conventional SLE management is lacking, the approach has been recommended for over a decade due to its potential to standardize care and improve patient outcomes. This framework represents a practical, consensus-driven tool for implementing T2T in real-world SLE management. It is designed to guide a broad spectrum of healthcare providers, including those beyond the specialized circle of lupus experts, in delivering structured, goal-oriented care to their patients.

O035 / #8

Topic: ***AS13 - Guidelines and Recommendations***

ABSTRACT CONCURRENT SESSION 05: EMERGING INSIGHTS ON THE MANAGEMENT OF LUPUS MANIFESTATIONS AND COMORBIDITIES
23-05-2025 1:40 PM - 2:40 PM

MULTIMODAL IMAGING APPROACH IN THE SUBCLINICAL DETECTION OF HYDROXYCHLOROQUINE-INDUCED RETINAL TOXICITY IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

Laura Pelegrín Colás[1], Olga Araújo[2], José Hernández Rodriguez[2], Gerard Espinosa[2], Ricard Cervera[2]
[1]Hospital Clinic, Ophthalmology, Barcelona, Spain, [2]Hospital Clinic, Autoimmune Diseases, Barcelona, Spain

Background/Purpose: To compare multimodal structural and functional diagnostic methods in patients with systemic lupus erythematosus (SLE) treated with hydroxychloroquine, to identify the best complementary approach for detecting subclinical retinal toxicity.

Methods: A cross-sectional, unicentric study was conducted on patients with SLE treated with hydroxychloroquine. Each patient underwent a comprehensive ophthalmic evaluation, comprising structural tests (spectral-domain optical coherence tomography (SD-OCT), en face OCT, en face OCT angiography (OCTA), fundus autofluorescence (FAF)) and functional tests (automated perimetry for visual field (VF) testing, multifocal electroretinography (mfERG)). A diagnosis of macular toxicity required the presence of abnormalities in at least one structural and functional test. The Kappa Concordance Index was used to assess the concordance among the different tests in detecting potential macular toxicity-associated alterations.

Results: Sixty-six patients with SLE (132 eyes) were consecutively enrolled. Four (6.1%) patients developed subclinical hydroxychloroquine-induced retinal toxicity without visual acuity impairment. The proportion of abnormal results was 24% for both en face OCT and en face OCTA. Regarding functional analysis, VF was less specific than mfERG in detecting subclinical retinal toxicity (VF specificity 47.5%). En face OCT and en face OCTA structural findings showed better concordance, with a kappa index >0.8, and both identified the same cases of toxicity as FAF.

Conclusions: Although structural OCT and VF are frequently used to screen for hydroxychloroquine-induced retinal toxicity, our findings suggest that a combination of mfERG, en face OCT and en face OCTA could improve the diagnostic accuracy for subclinical retinal damage. This study emphasises the importance of a multimodal

imaging strategy to promptly detect signs of hydroxychloroquine-induced retinal toxicity.

O036 / #542

Topic: ***AS15 - Lupus Nephritis-Clinical***

ABSTRACT CONCURRENT SESSION 06: LUPUS NEPHRITIS – CLINICAL OUTCOMES, PREDICTION AND THERAPY
23-05-2025 1:40 PM - 2:40 PM

CONTEMPORARY KIDNEY OUTCOMES AMONG PATIENTS WITH LUPUS NEPHRITIS IN THE UNITED STATES

Aakash Patel, Lingxiao Zhang, Baijun Zhou, Hyon Choi, April Jorge
Massachusetts General Hospital, Boston, United States of America

Background/Purpose: Lupus nephritis (LN) affects up to 50% of patients with systemic lupus erythematosus (SLE) and is associated with excess morbidity and mortality. Prior studies have demonstrated a disproportionate impact on Black patients. We sought to determine the burden of adverse kidney outcomes in a large, contemporary United States LN inception cohort.

Methods: We identified an SLE inception cohort from TriNetX, an electronic health record (EHR) database with patients from academic and non-academic medical centers across the United States. We included patients with SLE (≥2 ICD codes ≥30 days and ≤2 years apart) between January 2005 and August 2021 with at least 5 years of enrollment prior to the first ICD code. We identified patients with LN, defined as ≥1 LN code (ICD-10 M32.14 or M21.15), ≥2 nephritis codes (ICD-9 580-583, ICD-10 N00-N05), or ≥2 codes for proteinuria or kidney failure (ICD-9 791.0, 584-586, ICD-10 R80.9, N17-18) and a kidney biopsy. Patients were followed until the end of the study period, death, or disenrollment from the database. We assessed kidney health outcomes, including development of chronic kidney disease (CKD) stage ≥3 and end-stage kidney disease (ESKD), as well as the frequency and timing of kidney transplantation among those with LN-ESKD, according to various demographic subgroups such as sex and race/ethnicity.

Results: There were 24,957 SLE patients in the inception cohort, including 3748 (15%) with LN (**Table 1**). Early onset of LN occurring within six months of SLE diagnosis was observed in 61% of patients with LN, and the overall mean time to LN onset was 1.4 years (SD 2.3). Of those with LN, 1190 (32%) developed ESKD. Patients with LN were younger at onset (42.4 vs 48.9 years) and more commonly Black (42 vs 28%) or Hispanic (15 vs 9%) than overall SLE patients. Black individuals comprised nearly half of all patients with LN and ESKD. The 5-year risks of CKD stage ≥3 and ESKD among patients with LN were 68% and 35%, respectively. The risks of CKD stage ≥3 and ESKD were higher among Black than White individuals with LN (CKD stage ≥3 adjusted OR [aOR] 1.34 [95% CI 1.13-1.59] and ESKD aOR 1.25 [95% CI 1.05-1.49]) as well as males compared to females with LN (CKD stage ≥3 aOR 1.28 [95% CI 1.05-1.56] and ESKD

aOR 1.37 [95% CI 1.12-1.67]). Among those with LN-ESKD, the onset of ESKD occurred after a mean of 2.1 (SD 2.3) years following LN diagnosis, and 426 (36%) patients received a kidney transplant during the study period after a mean of 3.4 years (SD 3.2) from LN-ESKD onset (**Table 2**). Patients with early onset of LN had a shorter time to ESKD onset and kidney transplantation (P = 0.02 for both).

Conclusions: In this large EHR-based inception cohort of patients with SLE and LN in the United States, we observed a considerable risk of ESKD, especially among Black and male patients, occurring in around one-third of all patients with LN. Only slightly over one-third of patients with LN-ESKD ever received a kidney transplant. Limitations include the possibility of misclassification with the use of administrative codes. These findings highlight the need for strategies to improve LN and ESKD outcomes.

Table 1. Baseline Characteristics of Patients with Systemic Lupus Erythematosus, Lupus Nephritis, and Lupus Nephritis with End-Stage Kidney Disease

Characteristics	SLE	Lupus Nephritis	Lupus Nephritis-ESKD
N	24957	3748	1190
Age, years, mean (SD)	48.9 (15.9)	42.4 (16.8)	44.9 (15.3)
Age, years, n (%)			
<20	872 (3.5)	369 (9.9)	42 (3.5)
20-39	6388 (25.6)	1342 (35.8)	423 (35.5)
≥40	17482 (70.1)	2021 (53.9)	720 (60.5)
Female, n (%)	22527 (90.3)	3146 (84.0)	966 (81.2)
Race/Ethnicity, n (%)			
White	12816 (51.4)	1121 (29.9)	345 (29.0)
Black	7098 (28.4)	1574 (42.0)	557 (46.8)
Asian	428 (1.7)	115 (3.1)	30 (2.5)
Hispanic	2340 (9.4)	577 (15.4)	188 (15.8)
Other	2275 (9.1)	361 (9.6)	70 (5.9)
Geographic Region, n (%)			
East	6018 (24.1)	757 (20.2)	230 (19.3)
Midwest	4207 (16.9)	581 (15.5)	179 (15.0)
South	11295 (45.3)	1826 (48.7)	612 (51.4)
West	3429 (13.7)	583 (15.6)	168 (14.1)
Unknown	8 (0.0)	1 (0.0)	1 (0.1)
Year of diagnosis, mean (SD)	2016 (3)	2016 (4)	2015 (4)
Comorbidities, n (%)			
Type 2 diabetes	3732 (15.0)	592 (15.8)	283 (23.8)
Hypertension	8876 (35.6)	1494 (39.9)	799 (67.1)
Tobacco use	2854 (11.4)	309 (8.2)	157 (13.2)
Obesity	3242 (13.0)	404 (10.8)	163 (13.7)
CKD stage ≥3	5020 (20.1)	795 (21.2)	-
End-stage kidney disease	1602 (6.4)	629 (16.8)	-
Kidney transplant	381 (1.5)	378 (10.1)	324 (27.2)
Antiphospholipid syndrome	1552 (6.2)	235 (7.0)	111 (9.3)
Early LN, n (%)*	2272 (9.1)	2272 (60.6)	751 (63.1)
Duration of SLE prior to LN onset, mean (SD)	-	1.4 (2.3)	1.2 (2.1)

*Defined as meeting the lupus nephritis definition within 6 months after the first SLE code. CKD, chronic kidney disease

Table 2. Outcomes by Race/Ethnicity and Sex Among Patients with Lupus Nephritis with End-Stage Kidney Disease

	Mean (SD) duration between LN onset and ESKD onset	P-value (difference between means)	N (%) with LN-ESKD who received a kidney transplant	Mean (SD) time between LN-ESKD onset and kidney transplant	P-value (difference between means)
Overall LN-ESKD	2.1 (2.3)		426 (35.8)	3.4 (3.2)	
Race/Ethnicity					
White (ref)	2.1 (2.3)	-	126 (36.5)	2.9 (3.4)	-
Black	2.2 (2.3)	0.57	188 (33.8)	3.7 (3.3)	0.13
Asian	2.6 (2.6)	0.41	17 (56.7)	4.0 (2.2)	0.27
Hispanic	1.9 (2.3)	0.65	59 (31.4)	3.2 (3.1)	0.63
Other	2.2 (2.3)	0.77	36 (51.4)	2.7 (2.5)	0.74
Sex					
Male	2.1 (2.7)	0.78	73 (32.6)	2.7 (2.9)	0.09
Female (ref)	2.1 (2.2)	-	353 (36.5)	3.5 (3.2)	-
LN Onset*					
Early	1.9 (2.3)	0.02	235 (36.0)	3.0 (2.9)	0.02
Non-Early (ref)	2.4 (2.3)	-	191 (35.6)	3.9 (3.5)	-
Age at LN Onset, yrs					
Age <20	2.6 (3.4)	0.13	13 (25.5)	2.5 (2.3)	0.30
Age 20-39	2.1 (2.2)	0.83	155 (38.5)	3.4 (2.9)	0.85
Age ≥40 (ref)	2.1 (2.2)	-	258 (35.3)	3.5 (3.5)	-
Year of LN Diagnosis					
Before 2013 (ref)	2.9 (2.9)	-	154 (45.7)	4.0 (3.5)	-
After 2013	1.8 (1.9)	<0.01	272 (31.9)	3.0 (3.0)	0.02

*Defined as meeting the lupus nephritis definition within 6 months after the first SLE code. ESKD, end-stage kidney disease

O037 / #680

Topic: ***AS15 - Lupus Nephritis-Clinical***

ABSTRACT CONCURRENT SESSION 06: LUPUS NEPHRITIS – CLINICAL OUTCOMES, PREDICTION AND THERAPY
23-05-2025 1:40 PM - 2:40 PM

DOES BASELINE NEPHROTIC RANGE PROTEINURIA DETERMINE THE LONG-TERM OUTCOMES OF MEMBRANOUS LUPUS NEPHRITIS PATIENTS?

Fadi Kharouf, Pankti Mehta, Virginia Carrizo Abarza, Qixuan Li, Laura Whittall-Garcia, Dafna D Gladman, Zahi Touma
University of Toronto Lupus Clinic, Toronto, Canada

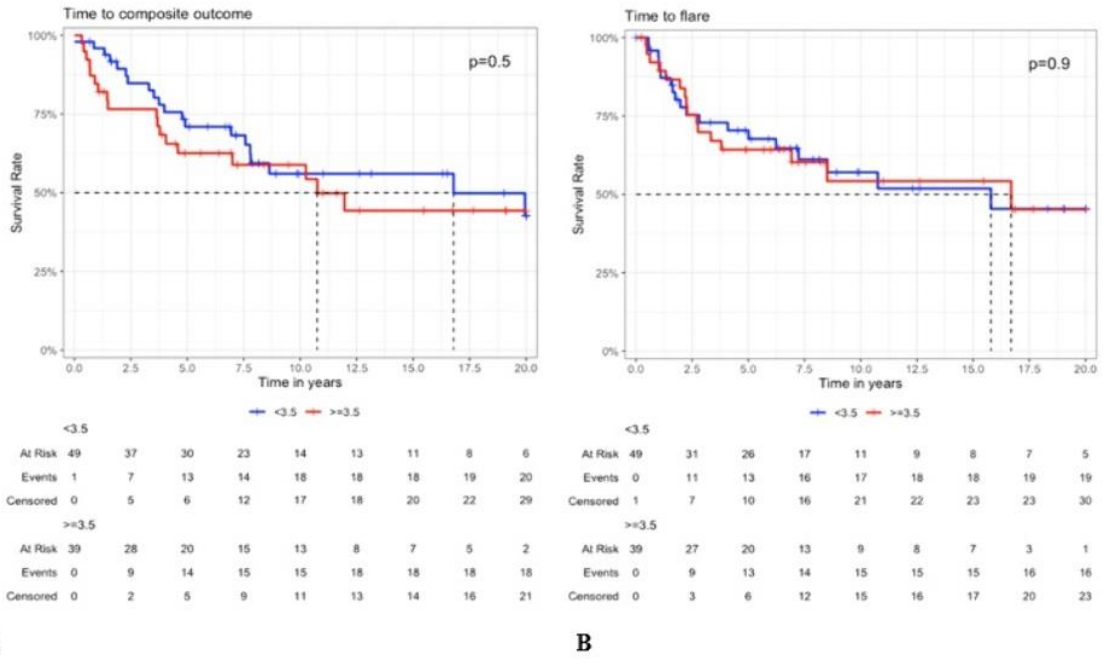
Background/Purpose: Management strategies for membranous lupus nephritis (MLN) are generally based on the severity of proteinuria. However, long-term outcomes comparing subnephrotic and nephrotic range proteinuria remain understudied. We explored whether baseline proteinuria level, subnephrotic or nephrotic, impacts long-term outcomes.

Methods: We conducted a retrospective study identifying patients with biopsy-proven MLN. Patients were categorized based on baseline proteinuria: subnephrotic (<3.5 g/day) or nephrotic (≥3.5 g/day). Long-term outcomes, including an adverse composite outcome (end-stage kidney disease, sustained ≥30% decline in eGFR, or death) and LN flares, were analyzed. Time-to-event outcomes were assessed using Kaplan-Meier curves, and associations were evaluated using Cox regression.

Results: Eighty-eight patients were included, with 49 (55.7%) in the subnephrotic group (median 1.5 g/day) and 39 (44.3%) in the nephrotic group (median 4.7 g/day). At baseline, the subnephrotic group had a longer time to LN onset, higher serum albumin, less diffuse podocyte effacement, and less frequent cyclophosphamide treatment (**Table 1**). No significant differences were noted in kidney function, urine sediment abnormalities, or histopathology. 38 patients (43.2%) experienced the adverse composite outcome, with no difference between groups (40.8% in the subnephrotic group vs. 46.2% in the nephrotic group, p=0.78]. Flares occurred in 35 patients (39.8%), with no difference between groups (38.8% in the subnephrotic group vs. 41.0% in the nephrotic group, p=1.00). Kaplan-Meier curves (**Figure 1**) and Cox proportional hazards model further confirmed these findings.

Table 1. Patient characteristics at the time of LN onset (baseline).

Variable		Overall (n=88)	Subnephrotic range proteinuria (n=49)	Nephrotic range proteinuria (n=39)	p-value
Age in years	Median [IQR]	37.3 [28.8, 46.0]	38.0 [29.5, 46.1]	36.3 [27.4, 45.7]	0.16
Sex, male	n (%)	16 (18.2)	6 (12.2)	10 (25.6)	0.18
SLE duration in years	Median [IQR]	4.6 [0.9, 11.9]	7.5 [1.4, 14.7]	1.9 [0.5, 9.7]	**0.01***
eGFR, mL/min/1.73 m^2	Median [IQR]	87.7 [67.2, 116.4]	91.2 [64.3, 115.3]	86.4 [71.3, 118.9]	0.69
Serum albumin, g/L	Median [IQR]	33.0 [25.0, 38.0]	36.0 [33.0, 39.0]	25.0 [22.8, 32.0]	**<0.01***
Low complement	n (%)	40 (46.0)	22 (44.9)	18 (47.4)	0.99
Positive anti-dsDNA	n (%)	45 (51.1)	25 (51.0)	20 (51.3)	1.00
Proteinuria, g/day	Median [IQR]	3.0 [1.4, 4.5]	1.5 [0.9, 2.2]	4.7 [4.0, 6.0]	**<0.01***
SLEDAI-2K	Median [IQR]	10.5 [8.0, 14.5]	11.0 [7.0, 12.0]	10.0 [8.0, 16.0]	0.49
SDI	Median [IQR]	1.0 [0.0, 1.0]	0.0 [0.0, 1.0]	1.0 [0.0, 1.8]	0.50
Biopsy changes, n=74	Endocapillary hypercellularity, n (%)	0 (0)	0 (0%)	0 (0)	NA
	Fibrinoid necrosis	0 (0)	0 (0)	0 (0)	NA
	Cellular/fibrocellular crescents, n (%)	0 (0)	0 (0)	0 (0)	NA
	Neutrophils/karyorrhexis, n (%)	0 (0)	0 (0)	0 (0)	NA
	Interstitial inflammation, n (%)	25 (33.3)	11 (27.5)	14 (40.0)	0.37
	Hyaline thrombi, n (%)	0 (0)	0 (0)	0 (0)	NA
	Total glomerulosclerosis, n (%)	35 (47.3)	19 (47.5)	16 (47.1)	1.00
	Fibrous crescents, n (%)	0 (0)	0 (0)	0 (0)	NA
	Interstitial fibrosis~, n (%)	50 (66.7)	26 (65.0)	24 (68.6)	0.94
	Tubular atrophy~, n (%)	47 (62.7)	26 (65.0)	21 (60.0)	0.84
	Diffuse FPE (>50%), n (%) (n=58)	46 (79.3)	21 (65.6)	25 (96.2)	**0.01***
Repeat biopsy	n (%)	26 (29.5)	13 (26.5)	13 (33.3)	0.65
NIH Activity index	Median [IQR]	0.0 [0.0, 1.0]	0.0 [0.0, 1.0]	1.0 [0.0, 1.0]	0.11
NIH Chronicity index	Median [IQR]	2.0 [0.0, 3.0]	2.0 [1.0, 3.0]	2.0 [0.0, 3.0]	0.72
Immunosuppressives used during the first year	Mycophenolate Mofetil, n (%)	41 (46.6)	23 (46.9)	18 (46.2)	1.00
	Cyclophosphamide, n (%)	8 (9.1)	1 (2.0)	7 (17.9)	**0.03***
	Azathioprine, n (%)	28 (31.8)	11 (22.4)	17 (43.6)	0.06
	Calcineurin inhibitors (Cyclosporine or Tacrolimus), n (%)	17 (19.3)	9 (18.4)	8 (20.5)	1.00
Antimalarial use	n (%)	61 (69.3)	37 (75.5)	24 (61.5)	0.24



A B

Figure 1 A-B. Kaplan-Meier curves showing the differences between subnephrotic and nephrotic range proteinuria in membranous lupus nephritis groups in:

A- Time to adverse composite outcome (end-stage kidney disease, a sustained ≥30% decline in eGFR, or death)
B- Time to subsequent lupus nephritis flare

Conclusions: No significant differences in renal disease characteristics or long-term outcomes were found between MLN patients with nephrotic and subnephrotic baseline proteinuria. These findings challenge current practices, suggesting a need for more individualized immunosuppressive treatment in MLN.

O038 / #692

Topic: ***AS15 - Lupus Nephritis-Clinical***

ABSTRACT CONCURRENT SESSION 06: LUPUS NEPHRITIS – CLINICAL OUTCOMES, PREDICTION AND THERAPY
23-05-2025 1:40 PM - 2:40 PM

FOCAL, DIFFUSE, AND MEMBRANOUS LESIONS IN LUPUS NEPHRITIS: PROGNOSTIC IMPLICATIONS FOR RENAL OUTCOMES

Maria Cuellar-Gutierrez[1,2], Jaime Flores-Gouyonnet[2], Gabriel Figueroa-Parra[2], Marta Casal Moura[2], Fernando C Fervenza[2], Cynthia Crowson[2], Sanjeev Sethi[3], Ali Duarte-Garcia[2]
[1]Hospital del Salvador, Rheumatology Division, Santiago, Chile, [2]Mayo Clinic, Rheumatology, Rochester, United States of America, [3]Mayo Clinic, Department Of Laboratory Medicine And Pathology, Rochester, United States of America

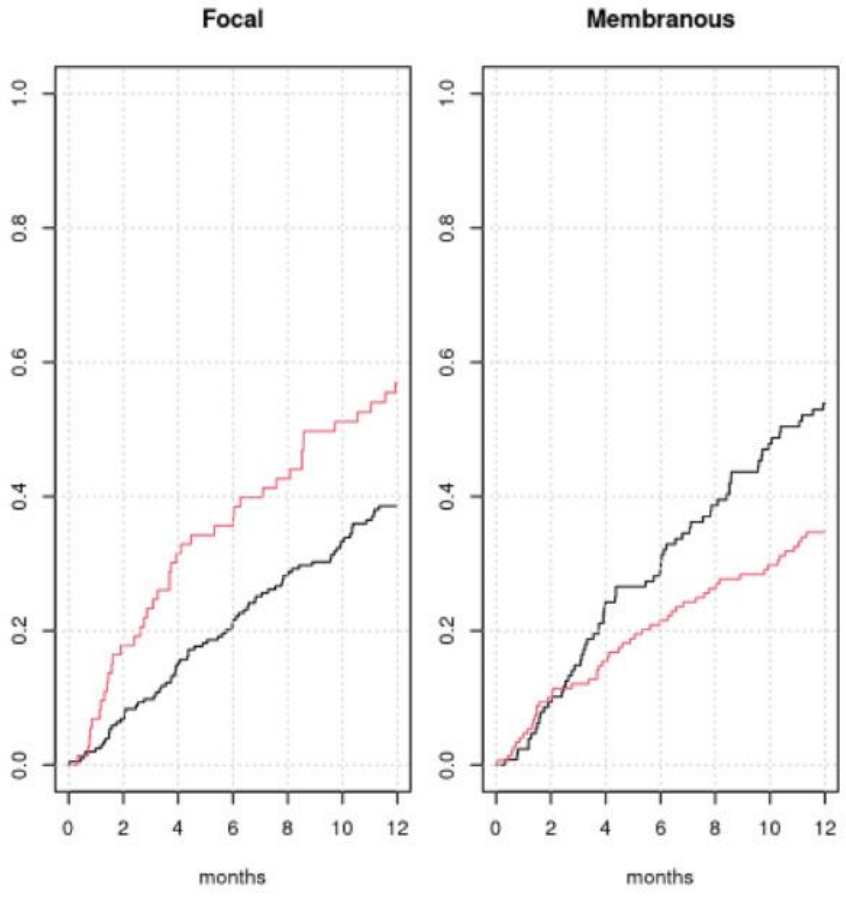
Background/Purpose: Lupus nephritis (LN) is major cause of morbidity in systemic lupus erythematosus, with histological classes potentially influencing clinical outcomes. We aimed to assess the predictive value of LN classes to inform prognosis and management.

Methods: We included patients with LN from Mayo Clinic between 1992 and 2023. Earliest kidney biopsy was index date. Patients were followed until July 2023, death, or loss follow-up. A nephropathologist (SS) reclassified LN classes using histological findings from light microscopy (LM) , immunofluorescence (IF), and electron microscopy (EM). Biopsies were categorized based on presence of mesangial, focal, diffuse, or membranous components. If a biopsy has more than one component, it was included in each of them. Focal and diffuse were mutually exclusive. Outcomes included proteinuria <500 mg/day and complete renal response (CRR) (proteinuria <500 mg/day and stabilization of glomerular filtration rate ± 20%) within 1 year, development of end-stage kidney disease (ESKD) and death. Stratified multivariable Cox proportional hazards regression models, adjusted for sex and age, were used to assess associations. Statistical significance defined p-values <0.05.

Results: Among 307 patients (median age: 34 years; 75% female; median follow-up: 11 years), 98.4% of biopsies had a mesangial component, 27% had a focal, 38.4% had a diffuse, and 49.5% had a membranous component. At 1 year, 47.5% of patients achieved proteinuria <500 mg/day, 43.4% CRR. The Table shows performance of components in predicting outcomes. Biopsies with focal component were significantly associated with higher rates of achieving proteinuria <500 mg/day (HR 1.74 [95% CI, 1.21–2.50]) and CRR (HR 1.82 [95% CI, 1.24–2.66]). A diffuse component was not significantly associated with either proteinuria <500 mg/day (HR 0.98 [95% CI, 0.69–

1.40]) or CRR (HR 1.00 [95% CI, 0.69–1.44]), though confidence intervals suggest near-significant association with achieving proteinuria <500 mg/day. A membranous component was associated with lower likelihood of achieving proteinuria <500 mg/day (HR 0.64 [95% CI, 0.45–0.90]) and CRR (HR 0.59 [95% CI, 0.41–0.84]). Cumulative incidence curves for CRR are in, [Figure 1].

Figure 1. Kaplan Meier curves for Complete renal response (CRR) for focal and membranous component. Patients with focal component in the biopsy are more likely to experience CRR, whereas patients with membranous component are less likely. Red line: Having the mentioned component (Focal or membranous), Black: Not having the mentioned component (Focal or membranous).



During follow-up, 33 patients died (10.7%), 60 developed ESKD (19.5%). No components were associated with mortality. Membranous component was associated with lower risk of ESKD (HR 0.58 [95% CI, 0.35–0.90]), while focal (HR 0.65 [95% CI, 0.35–1.23]) and diffuse (HR 1.65 [95% CI, 0.98–2.77]) were not predictive, though diffuse component trended toward significance. Cumulative incidence curves for ESKD are in, [Figure 2].

Figure 2: Kaplan Meier curves for end stage kidney disease (ESKD) for diffuse and membranous component. Diffuse component in the biopsy is not predicting ESKD, whereas membranous component tends to be protective for developing ESKD. Red line: Having the mentioned component (Diffuse or membranous), Black: Not having the mentioned component (Diffuse or membranous).

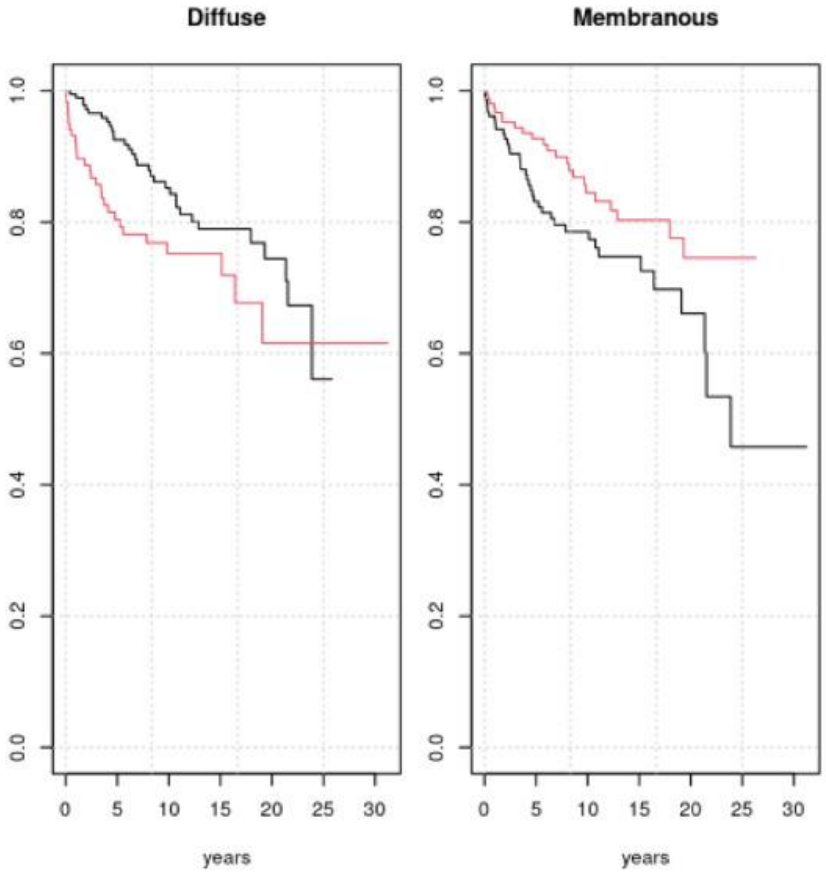


Table. Hazard ratios of outcomes for variables.

	Prot <500 HR (95%CI)	**CRR HR (95%CI)**	**ESKD HR (95%CI)**	**Death HR (95%CI)**
Focal any	**1.74 (1.21, 2.50)***	**1.82 (1.24, 2.66)***	0.65 (0.35, 1.23)	1.07 (0.49, 2.33)
Diffuse any	0.98 (0.69, 1.40)	1.00 (0.69, 1.44)	1.65 (0.98, 2.77)	0.95 (0.45, 2.02)
Membranous any	**0.64 (0.45, 0.90)***	**0.59 (0.41, 0.84)***	**0.58 (0.35, 0.90)***	0.76 (0.37, 1.57)

Prot <500: proteinuria <500mg/day, **CRR:** Complete renal response, **ESKD**: End Stage kidney disease, **HR**: Hazard ratio, ***=p<0.05.**

Conclusions: Mesangial components are present in nearly all biopsies. Focal components are associated with better short-term renal outcomes, including higher rates of CRR. Membranous components predict both a lower likelihood of CRR and a reduced risk of developing ESKD. Consequently, patients with mixed lesions may take longer to achieve CRR compared to those with pure proliferative GN. Our study also demonstrates patients with focal lesions have better prognosis than those with diffuse. These underscore the importance of detailed histological analysis in LN biopsies to guide prognosis and therapeutic.

O039 / #695

Topic: ***AS15 - Lupus Nephritis-Clinical***

ABSTRACT CONCURRENT SESSION 06: LUPUS NEPHRITIS – CLINICAL OUTCOMES, PREDICTION AND THERAPY
23-05-2025 1:40 PM - 2:40 PM

EFFICACY AND SAFETY OF RITUXIMAB (RTX) IN REFRACTORY LUPUS NEPHRITIS (LN) FROM REAL-WORLD LOOPS REGISTRY

Masanobu Ueno, Shingo Nakayamada, Ippei Miyagawa, Hiroaki Tanaka, Satoshi Kubo, Yusuke Miyazaki, Yasuyuki Todoroki, Yurie Kanda, Yuya Fujita, Hidenori Sakai, Yoshiya Tanaka
University of Occupational and Environmental Health, Japan, The First Department Of Internal Medicine, Kitakyushu, Japan

Background/Purpose: In 2023, Rituximab (RTX) therapy for lupus nephritis was approved in Japan. However, the efficacy and safety in real-world clinical practice have not been validated. This study aimed to assess the efficacy and safety of RTX for LN in real-world clinical practice.

Methods: Patients with LN who received remission induction therapy with high- or moderate-dose GC or GC pulse, combined with HCQ+RTX (RTX group, n=33), +MMF (MMF group, n=77), or +CYC group (CYC group, n=24) after May 2016 (when MMF was approved in Japan) were included. The efficacy and safety were compared among groups. The primary endpoint was the achievement rate of Complete Renal Response (CRR) and uPCR <1.0 at week 52. The secondary endpoints were retention rate, adverse events, and GC-sparing effect. In addition, peripheral blood immunophenotyping was performed on age- and gender-matched HCs and patients with LN. In patients with LN, immune phenotyping was also conducted before and after treatment.

Results: Treatment retention was 90.9% (30/33) in the RTX group, 90.9% (70/77) in the MMF group, and 70.8% (17/24) in the CYC group. The most common adverse events were infusion reactions (27.3%) in RTX and infections in MMF (32.4%) and CYC (58.3%). SLEDAI and BILAG scores significantly decreased in all groups. CRR achievement rates were 39.4% (RTX), 48.1% (MMF), and 37.5% (CYC), and uPCR <1.0 rates were 82.7% (RTX), 87.0% (MMF), and 81.3% (CYC) , with no significant differences among the groups. GC-sparing effects were also similar across the groups (RTX: -87.8%, MMF: -84.4%, CYC: -86.7%). Immunophenotyping revealed that class-switched memory B cells (CM B cells) and plasmocytes were elevated in SLE patients compared to healthy controls (HCs). In the RTX group, naïve B cells, CM B cells, and plasmocytes were found to have disappeared at 26 weeks. In cases achieving CRR in the RTX group, CM B cells and plasmocytes remained undetectable at 52 weeks, whereas in non-CRR cases, they

showed a re-increase. Changes in T cells were not associated with treatment efficacy in the RTX group. In the MMF and IVCY groups, naïve B cells, CM B cells, and plasmocytes were significantly decreased at week 52; however, this decrease was not associated with treatment efficacy. On the other hand, in cases achieving CRR in the MMF and IVCY groups, activated $CD4^+$ T cells and activated Th1 cells were significantly reduced.

Conclusions: Immunosuppressive drugs and RTX had different effects on the immune phenotype. RTX can be an effective treatment option for LN in real-world clinical practice.

O040 / #227

Topic: ***AS15 - Lupus Nephritis-Clinical***

ABSTRACT CONCURRENT SESSION 06: LUPUS NEPHRITIS – CLINICAL OUTCOMES, PREDICTION AND THERAPY
23-05-2025 1:40 PM - 2:40 PM

CLINICAL AND HISTOLOGICAL PREDICTORS OF RENAL FUNCTION LOSS IN LUPUS NEPHRITIS: RESULTS FROM THE ACCELERATING MEDICINES PARTNERSHIP IN RA/SLE NETWORK

Shangzhu Zhang[1], Laurence Magder[2], Daniel Goldman[1], Peter Izmirly[3], Michael H Belmont[3], Richard Furie[4], Noa Schwartz[5], Chaim Putterman[5], Jennifer Barnas[6], Jennifer Anolik[6], Sarah French[7], Maria Dall'Era[7], Judith James[8], Joel Guthridge[8], Jeffrey B Hodgin[9], Dawit Demeke[9], The Accelerating Medicines Partnership In Ra/Sle Network[10], Jill Buyon[3], Michelle Petri[1], Andrea Fava[1]
[1]John Hopkins University School of Medicine, Division of Rheumatology, Baltimore, United States of America, [2]University of Maryland School of Medicine, Baltimore, United States of America, [3]New York University School of Medicine, Medicine, New York, United States of America, [4]Northwell Health, Great Neck, United States of America, [5]Albert Einstein College of Medicine, Department Of Medicine, Bronx, United States of America, [6]University of Rochester Medical Center, Division Of Rheumatology, Rochester, United States of America, [7]University of California, San Francisco, San Francisco, United States of America, [8]Oklahoma Medical Research Foundation, Oklahoma City, United States of America, [9]University of Michigan, Department Of Pathology, Ann Arbor, United States of America, [10]Multiple institutions, multiple, United States of America

Background/Purpose: Kidney survival is the ultimate outcome in lupus nephritis (LN), but predictors remain inadequately studied due to the need for long-term follow up. This study aimed to identify clinical and histological predictors of kidney survival in LN.

Methods: The Accelerating Medicines Partnership (AMP) enrolled patients undergoing a clinically indicated (UPCR >0.5) kidney biopsy with resultant histology class II, III, IV, and/or V lupus nephritis (LN). Clinical and demographic features were collected from the time of diagnostic biopsy. Response was defined at 1 year for patients with baseline UPCR >1. Histological features were centrally scored. Kidney function loss was defined as a sustained 40% decline in estimated glomerular filtration rate (eGFR) or progression to end stage kidney disease (ESKD). A Cox-proportional hazard model was employed to identify predictors.

Results: We included 172 patients with a median follow-up time of 4.6 years (range 0.5-7.8), of whom 153 (89%) had >3 years follow up. Clinical and demographic features are

summarized in Table 1. A third of patients (56/172) developed eGFR loss with a median time to event of 2.6 years (range 0.13-7.1). Predictors of eGFR loss at time of biopsy included lower eGFR (especially eGFR <30 ml/min, HR 5.4), repeat biopsy status (HR 2.5), and NIH Chronicity Index (histological damage, HR 1.3 per unit) (Table 1). Sex, race, age, BMI, proteinuria, ISN class, NIH Activity Index, C3, C4, and anti-dsDNA were not associated with eGFR loss. Among histological features, an NIH Chronicity Index >2 (HR 2), glomerulosclerosis (HR 1.9), interstitial fibrosis (HR 2), tubular atrophy (HR 1.9), and interstitial inflammation (HR 2-but p=0.06), but not fibrous crescents or any of the NIH Activity Index glomerular features, were associated with eGFR loss (Table 1). Lack of clinical response at 3, 6, or 12 months was associated with future eGFR loss (Figure 1). Partial response at 12 months had higher risk of eGFR loss compared to complete response (HR 10.7), but lower than no response (HR 19). Reductions of UPCR >25% at 3 and >50% at 6 months were protective (HR 0.44-but p=0.11 and 0.3, respectively). Four patients with UPCR <0.5 at 1 year developed eGFR loss (1.8/100 person years).

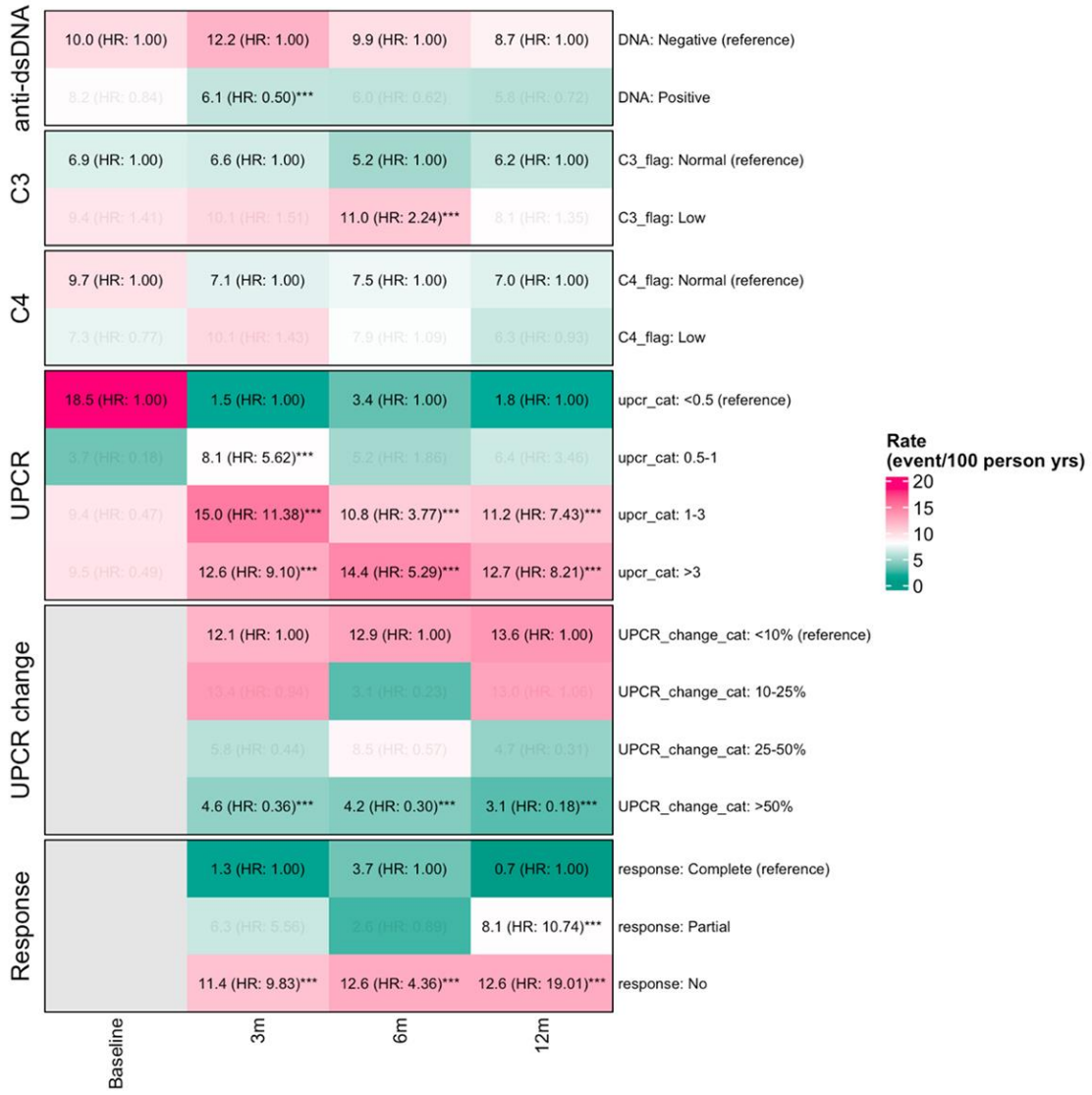
Table 1. Association of baseline clinical, demographic, and histological features with GFR loss.

Variable	Events Number	Total Number	Person years	Rate per 100 person-years	HR	CI	P value[a]
Sex							
Female (reference)	42	142	538.3	7.8	1		
Male	14	30	121.4	11.5	1.5	[0.82-2.75]	0.19
Race							
Asian (reference)	8	26	97.2	8.2	1		
Black	22	70	294.7	7.5	0.88	[0.39-1.98]	0.75
White	14	47	165.5	8.5	1.07	[0.45-2.56]	0.87
Other	9	23	86.3	10.4	1.27	[0.49-3.3]	0.62
Age, years	56	172	659.7	8.5	0.99	[0.97-1.02]	0.64
Age groups, years							
<30 (reference)	19	57	202.2	9.4	1		
30-50	29	93	358.5	8.1	0.85	[0.47-1.53]	0.59
>50	8	22	99.1	8.1	0.82	[0.36-1.89]	0.65
BMI	49	158	614.6	8	0.99	[0.95-1.04]	0.78
Anti-dsDNA							
Negative (reference)	16	42	172.8	9.3	1		
Positive	33	111	416.5	7.9	0.88	[0.48-1.6]	0.67
C3							
Normal (reference)	17	60	246.2	6.9	1		
Low	36	104	383.1	9.4	1.41	[0.79-2.51]	0.25
C4							
Normal (reference)	29	78	299.7	9.7	1		
Low	24	86	329.6	7.3	0.77	[0.45-1.32]	0.34
UPCR	46	151	569.2	8.1	1.06	[0.95-1.18]	0.32
UPCR groups							
<0.5 (reference)	1	2	5.4	18.5	1		
0.5-1	5	29	136.7	3.7	0.18	[0.02-1.53]	0.12
1-3	28	81	296.9	9.4	0.47	[0.06-3.46]	0.46
>3	20	57	210.4	9.5	0.49	[0.07-3.66]	0.49
Serum creatinine, mg/dl	56	171	656.5	8.5	1.64	[1.26-2.12]	**<0.001**
eGFR, mL/min/1.73 m²	56	172	659.7	8.5	0.99	[0.98-1]	**<0.001**
eGFR groups, mL/min/1.73 m²							
>90 (reference)	27	91	356.4	7.6	1		
60-90	10	38	164.2	6.1	0.82	[0.4-1.71]	0.6
30-60	11	32	114.8	9.6	1.34	[0.66-2.71]	0.42
<30	8	11	24.3	32.9	5.44	[2.4-12.32]	**<0.001**

Variable	Events Number	Total Number	Person years	Rate per 100 person-years	HR	CI	P value[a]
First or repeat biopsy							
First (reference)	10	61	239.5	4.2	1		
Not first	41	101	384.9	10.7	2.51	[1.26-5.03]	**0.01**
Histological features							
ISN Class							
I/II	3	8	32.4	9.3	1.04	[0.31-3.53]	0.95
Membranous (reference)	19	52	207.4	9.2	1		
Mixed Proliferative	14	53	214.6	6.5	0.72	[0.36-1.44]	0.36
Proliferative	20	59	205.3	9.7	1.09	[0.58-2.05]	0.78
NIH Activity Index	49	151	581.2	8.4	1.02	[0.96-1.08]	0.55
NIH Chronicity Index	49	152	585.4	8.4	1.33	[1.17-1.5]	**<0.001**
NIH Chronicity Index > 0							
No (reference)	3	19	63.2	4.7	1		
Yes	46	133	522.2	8.8	1.79	[0.56-5.76]	0.33
NIH Chronicity Index > 1							
No (reference)	7	41	146.2	4.8	1		
Yes	42	111	439.2	9.6	1.98	[0.89-4.4]	0.09
NIH Chronicity Index > 2							
No (reference)	11	60	228.7	4.8	1		
Yes	38	92	356.6	10.7	2.23	[1.13-4.38]	**0.02**
NIH Chronicity Index > 3							
No (reference)	18	88	356.8	5	1		
Yes	31	64	228.6	13.6	2.81	[1.55-5.08]	**<0.001**
NIH Chronicity Index > 4							
No (reference)	25	110	451.6	5.5	1		
Yes	24	42	133.8	17.9	3.45	[1.95-6.11]	**<0.001**
Endocapillary Hypercellularity	25	82	324.4	7.7	1.16	[0.77-1.75]	0.49
Neutrophils. Karyorrhexis	25	82	324.4	7.7	0.74	[0.28-1.92]	0.53
Fibrinoid. Necrosis	25	82	324.4	7.7	0.77	[0.2-2.91]	0.69
Wire Loops or Hyaline Thrombi	25	82	324.4	7.7	0.72	[0.29-1.78]	0.47
Cellular or Fibrocellular Crescents	25	82	324.4	7.7	1.23	[0.76-2]	0.39
Interstitial Inflammation	25	82	324.4	7.7	2.02	[0.96-4.24]	0.06
Glomerulosclerosis Score	25	82	324.4	7.7	1.88	[1.19-2.96]	**0.01**
Fibrous Crescents	25	82	324.4	7.7	2.36	[0.88-6.35]	0.09
Tubular Atrophy	25	82	324.4	7.7	1.96	[1.23-3.12]	**<0.001**
Interstitial Fibrosis	25	82	324.4	7.7	1.89	[1.22-2.94]	**<0.001**

eGFR, estimated glomerular filtration rate; HR, Hazard Ratio; ISN, International Society of Nephrology; LN, lupus nephritis; UPCR, urine protein-creatinine ratio.
a Based on Cox proportional hazard model.

Figure 1. Association of longitudinal clinical features with GFR loss



Heatmap displaying rates of adverse events per 100 person-years and hazard ratios (HR) based on time to event analysis (Cox proportional hazard model) for GFR loss at 4 time points (baseline and 3, 6, and 12 months). For non-baseline timepoints, events before the timepoint were censored. UPCR change is categorized based on the percentage decrease in UPCR from baseline to each follow-up time point. Complete response was defined as a UPCR ≤0.5, normal serum creatinine (≤1.3 mg/dL) or, if abnormal, ≤125% of baseline, and prednisone taper to ≤10 mg/day. Partial response was defined by >50% reduction in UPCR without meeting UPCR criterion for complete response, normal creatinine (≤1.3 mg/dL) or, if abnormal, ≤125% of baseline, and prednisone dose ≤15 mg/day. ***P < 0.05. dsDNA, double-stranded DNA; LN lupus nephritis; UPCR, urine protein-creatinine ratio. The color scale was centered (white) at the unadjusted rate for the whole population.

Conclusions: Low baseline eGFR and histological damage, but not activity or ISN class, predicted eGFR loss. Improvement of UPCR was associated with lower risk of eGFR

loss, though eGFR loss still occurred in patients in clinical remission (UPCR <0.5) at 1 year. **Acknowledgments** This work was funded by the Plank Family Foundation and the Jerome L. Greene Foundation. The Hopkins Lupus Cohort is supported by NIH R01-DK-134625. Additionally, this research was supported by the Accelerating Medicines Partnership® Rheumatoid Arthritis and Systemic Lupus Erythematosus (AMP® RA/SLE) Network, a public-private partnership involving AbbVie Inc., Arthritis Foundation, Bristol-Myers Squibb Company, Foundation for the National Institutes of Health, GlaxoSmithKline, Janssen Research and Development, LLC, Lupus Foundation of America, Lupus Research Alliance, Merck & Co., Inc. Sharp & Dohme Corp., National Institute of Allergy and Infectious Diseases, National Institute of Arthritis and Musculoskeletal and Skin Diseases, Pfizer Inc., Rheumatology Research Foundation, Sanofi, and Takeda Pharmaceuticals International, Inc. The AMP Network aims to develop new methods for identifying and validating promising biological targets for diagnostics and drug development. Funding was provided through grants from the National Institutes of Health (UH2-AR067676, UH2-AR067677, UH2-AR067679, UH2-AR067681, UH2-AR067685, UH2-AR067688, UH2-AR067689, UH2-AR067690, UH2-AR067691, UH2-AR067694, and UM2-AR067678).

O041 / #709

Topic: ***AS15 - Lupus Nephritis-Clinical***

ABSTRACT CONCURRENT SESSION 06: LUPUS NEPHRITIS – CLINICAL OUTCOMES, PREDICTION AND THERAPY
23-05-2025 1:40 PM - 2:40 PM

PREDICTIVE VALUE OF CHRONIC HISTOLOGIC CHANGES IN LUPUS NEPHRITIS

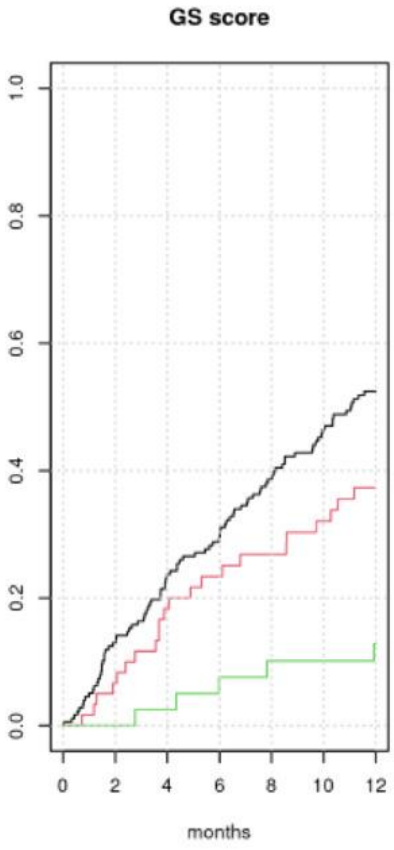
Maria Cuellar-Gutierrez[1,2], Jaime Flores-Gouyonnet[1], Gabriel Figueroa-Parra[1], Marta Casal Moura[1], Fernando C Fervenza[1], Cynthia Crowson[1], Ali Duarte-Garcia[1], Sanjeev Sethi[3]
[1]Mayo Clinic, Rheumatology, Rochester, United States of America, [2]Hospital del Salvador, Rheumatology Division, Santiago, Chile, [3]Mayo Clinic, Department Of Laboratory Medicine And Pathology, Rochester, United States of America

Background/Purpose: The Mayo Clinic Chronicity Score (MCCS) is a tool to assess the chronicity of renal histology in glomerulopathies. This tool includes arteriosclerosis (AE), a chronic vascular lesion, and has not been evaluated in lupus nephritis (LN). Our objective was to evaluate the predictive value of the individual components of the International Society of Nephrology/Renal Pathology Society and MCCS in LN.

Methods: LN patients from Mayo Clinic between 1992 and 2023 were included. The earliest kidney biopsy was index date. Follow-up was until July 2023, death or loss follow-up. Biopsy reports were reviewed by a nephropathologist and chronic lesions reclassified (glomerulosclerosis [GS], interstitial fibrosis [IF], tubular atrophy [TA], arteriosclerosis [AE], and fibrous crescents [FC]). The outcomes were proteinuria <500 mg/day and complete renal response (CRR) within 1-year, end-stage kidney disease (ESKD), and death. We used stratified multivariable proportional hazards regression adjusted for sex and age. P-values <0.05 were statistically significant.

Results: We included 307 patients (median age, 34 years; 75% female; median follow-up, 11 years). The majority had Class III, IV. FC were in 4.9%, AE in 12%. Table shows hazard ratios of proteinuria<500mg/day, CRR, ESRD, and death for different variables of interest.
At one year, 47.5% had proteinuria <500 mg/day and 43.4% CRR. Those with grade 2-3 of GS (HR 0.21 [0.09, 0.48] and grade 2-3 IFTA (HR 0.14 [0.05, 0.39] were less likely to achieve proteinuria <500 mg/day. Grade 2-3 of GS (HR 0.19 [0.08, 0.48]) and grade 2-3 IFTA (HR 0.16 [0.06, 0.44] were also less likely to achieve CRR. [Figure 1] shows increasing grades of GS is associated with a lower chance of
CRR.

Figure 1: Kaplan Meier curve for complete renal response (CRR) for glomerulosclerosis (GS) score. Black line: GS grade 0, red: GS grade 1, green: GS grades 2-3. Increasing GS is associated with a lower chance of CRR.



Similarly, AE (HR 0.44 [0.21, 0.91], for proteinuria <500 mg/day, HR 0.37 [0.16, 0.84], for CRR) was associated with a reduced likelihood of achieving the outcomes. During follow-up, 33 patients died, and 60 developed ESKD. No variables were associated with mortality. Grade 2-3 GS (HR 9.28 [4.91, 17.54], grade 2-3 IFTA (HR 20.10 [10.08, 40.08]), and the presence of AE (HR 3.56 [1.87, 6.78]) were associated with an increased ESKD. [Figure 2] shows increasing grades of GS is associated with a greater chance of ESKD.

Figure 2: Kaplan Meier curve for end stage kidney disease (ESKD) for glomerulosclerosis (GS) score. Black line: GS grade 0, red: GS grade 1, green: GS grades 2-3. Increasing GS is associated with greater hazard of ESKD

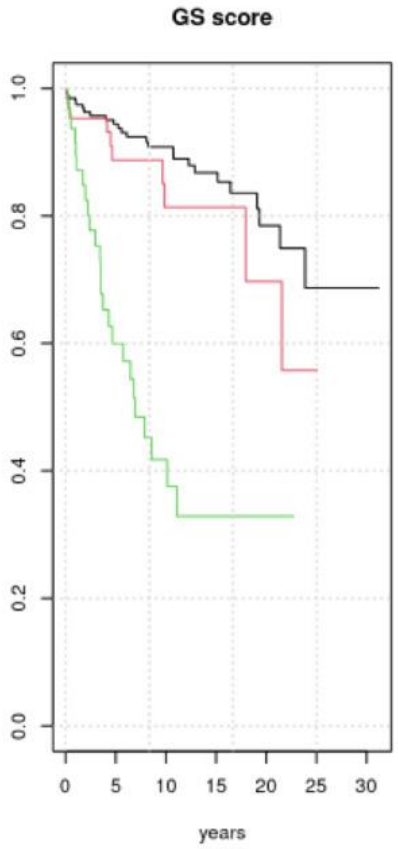


Table. Hazard ratios of proteinuria<500mg/day, CRR, ESKD, and death for variables.

Element	Prot <500 HR (95%CI)	CRR HR (95%CI)	ESKD HR (95%CI)	Death HR (95%CI)
GS grade 1	0.68 (0.43, 1.08)	0.68 (0.42, 1.10)	1.94 (0.91, 4.13)	1.47 (0.57, 3.77)
GS grade 2-3	**0.21 (0.09, 0.48)***	**0.19 (0.08, 0.48)***	**9.28 (4.91, 17.54)***	2.15 (0.93, 4.98)
IFTA grade 1	**0.57 (0.37, 0.88)***	**0.54 (0.34, 0.86)***	**3.44 (1.70, 6.96)***	1.26 (0.51, 3.12)
IFTA grade 2-3	**0.14 (0.05, 0.39)***	**0.16 (0.06, 0.44)***	**20.10 (10.08, 40.08)***	1.89 (0.79, 4.52)
FC grade 1-3	0.87 (0.38, 1.98)	1.02 (0.44, 2.34)	1.05 (0.25, 4.34)	0.00 (0.00, Inf)

AE score 1	**0.44 (0.21, 0.91)***	**0.37 (0.16, 0.84)***	**3.56 (1.87, 6.78)***	1.10 (0.41, 2.90)

Prot <500: Proteinuria <500mg/day, **CRR:** Complete renal response, **ESKD**: End Stage kidney disease, **HR**: Hazard ratio, **GS**: Glomerulosclerosis, **IFTA**: Interstitial fibrosis and tubular atrophy, **FC**: Fibrous crescent, **AE**: Arteriosclerosis. ***=p<0.05.**

Conclusions: GS, IFTA, AE are independently associated with outcomes in LN. FC is rare finding. The MCCS included all the chronic histologic elements associated with outcomes in LN.

O042 / #592

Topic: ***AS18 - Paediatric SLE***

ABSTRACT CONCURRENT SESSION 07: COGNITION IMPAIRMENT IN SLE – RECENT ADVANCEMENT AND EMERGING RESEARCH
23-05-2025 1:40 PM - 2:40 PM

INVESTIGATING THE RELATIONSHIP BETWEEN ALTERED STRUCTURAL BRAIN METRICS (VOLUME, CORTICAL THICKNESS AND SURFACE AREA) AND COGNITIVE PERFORMANCE IN CHILDHOOD-ONSET SYSTEMIC LUPUS ERYTHEMATOSUS

Sarah Mossad[1], Santiago Arciniegas[2], Tala El Tal[3], Lawrence Ng[4], Paris Moaf[4], Asha Jeyanathan[2], Joanna Law[2], Helen Branson[5], Adrienne Davis[6], Linda Hiraki[7], Deborah Levy[8], Ashley Danguecan[9], Andrea Knight[10]
[1]The Hospital for Sick Children, Department Of Psychology, Toronto, Canada, [2]The Hospital for Sick Children, Neurosciences And Mental Health, Research Institute, Toronto, Canada, [3]Children's Hospital for Eastern Ontario, Pediatrics, Division Of Rheumatology And Dermatology, Ottawa, Canada, [4]The Hospital for Sick Children, Division Of Rheumatology, Toronto, Canada, [5]The Hospital for Sick Children, Diagnostic Imaging, Toronto, Canada, [6]The Hospital for Sick Children, Emergency Medicine, Toronto, Canada, [7]Division of Rheumatology, The Hospital for Sick Children; Genetics and Genome Biology, SickKids Research Institute, Toronto, Canada, [8]Division of Rheumatology, The Hospital for Sick Children; Child Health Evaluative Sciences, SickKids Research Institute, Toronto, Canada, [9]The Hospital for Sick Children, Psychology, Toronto, Canada, [10]The Hospital for Sick Children, Rheumatology, Toronto, Canada

Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic, autoimmune, and inflammatory disease affecting nearly 3.41 million individuals worldwide. SLE is characterised by overproduction of autoantibodies causing inflammation in any organ system including the central nervous system (CNS), resulting in cognitive impairment. Childhood-onset SLE (cSLE) is associated with higher frequency of CNS involvement and cognitive difficulties. However, the neural underpinnings of these cognitive difficulties remain poorly understood. The objectives of this study are to identify differences in regional brain volume, cortical thickness and surface area in cSLE compared to age and sex-matched typically developing controls using structural magnetic resonance imaging (sMRI), and determine the association between brain structure and cognitive outcome in cSLE.

Methods: Participants (age 12-16years), diagnosed with SLE meeting classification criteria and age and sex-matched healthy controls were recruited from January 2020–September 2023. Children completed a battery of neuropsychology tasks measuring attention (Conner's Continuous Performance Test), working memory (Digit Span task;

Weschler intelligence scale for Children: 5th Ed.), inhibition, cognitive flexibility and processing speed (Color-Word Interference task; Delis-Kaplan Executive Function System) and each score was standardized using age-based norms. T1-weighted images were also obtained for each subject and group differences in brain volume, cortical thickness and surface area were computed in FreeSurfer. Between group differences in cognitive performance were tested using two-tailed t-tests. Correlations between cognitive performance and structural measures were computed using Spearman's rank correlation coefficient. Group differences in the proportion of cases meeting clinical criteria for cognitive difficulties (defined as scores ≥1.5 SD below the mean) were tested using χ^2 tests. All results are reported as significant at $p<0.05$.

Results: Thirty-two cSLE patients and 32 healthy controls participated. There were no differences in age, sex, or household income between groups. The mean disease duration for cSLE patients was 3.6years±2.8. On average, cSLE patients performed significantly worse on inhibition ($p=0.020$) and processing speed tasks ($p=0.004$). More cSLE patients than controls met clinical cut-offs for cognitive difficulties in the processing speed domain ($p=0.030$). Neuroimaging results showed decreased volume, cortical thickness and surface area in the cSLE group (controls>cSLE) in several regions including the bilateral superior temporal gyrus (STG), left superior parietal gyrus, middle cingulate gyrus, right middle frontal gyrus. Decreased volume and surface area in the right STG were significantly correlated with worse cognitive performance. Decreased volume and cortical thickness in the anterior/posterior cingulate gyrus were significantly correlated with worse cognitive performance. Regions of increased surface area, volume and cortical thickness in cSLE>controls were also found and included the bilateral insula, right superior parietal gyrus, right inferior temporal gyrus, left inferior/superior frontal gyrus. Increased volume in the left inferior frontal gyrus was correlated with worse cognitive performance.

Conclusions: This study highlights the importance of neuropsychological assessment and utilizing advanced MRI methods to assess for CNS involvement in cSLE. Neuroimaging results revealed that specific areas of altered volume, cortical thickness and surface area were associated with decreased cognitive performance in cSLE. These results inform our understanding of the potential neural mechanisms underlying cognitive impairment in this population, which can be used to develop more targeted neuropsychological assessment and intervention approaches for the purposes of treatment planning.

O043 / #45

Topic: *AS05 - CNS Lupus*

ABSTRACT CONCURRENT SESSION 07: COGNITION IMPAIRMENT IN SLE – RECENT ADVANCEMENT AND EMERGING RESEARCH
23-05-2025 1:40 PM - 2:40 PM

INTERNATIONAL EFFORT IN HARMONISING COGNITIVE IMPAIRMENT RESEARCH IN SYSTEMIC LUPUS ERYTHEMATOSUS

Michelle Barraclough[1,2], Shane Mckie[3], Leticia Rittner[4], Andrea Knight[5], Patti Katz[6], John Hanly[7], Alexandra Legge[7], Meggan Mackay[8], Chrisanna Dobrowolski[9], Hermine Brunner[10], Ekemini Ogbu[11], Chris Wincup[12], Marcello Govoni[13], Alessandra Bortoluzzi[13], Ettore Silvagni[13], Lesley Ruttan[14], Kathleen Bingham[14], Robin Green[14], Carmela Tartaglia[14], Susan Lee[15], John Fisk[16], Kamil Uludag[14,17], Chris Tang[18], Diana Valdés Cabrera[19], Erik Anderson[20], Mark Difrancesco[21], Alberta Hoi[22], Sudha Raghunath[22], Elizabeth Kozora[23], Xiang He[24], Rebecca Elliott[3], Ben Parker[2,25], Ian Bruce[2,25,26], Zahi Touma[14,17], Simone Appenzeller[4]
[1]Centre for Musculoskeletal Research, The University of Manchester, Faculty Of Biology, Medicine And Health, Manchester, United Kingdom, [2]NIHR Manchester Biomedical Research Centre, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, United Kingdom, [3]The University of Manchester, Manchester, United Kingdom, [4]University of Campinas, Campinas, Brazil, [5]The Hospital for Sick Children, Toronto, Canada, [6]University of California San Francisco, San Francisco, United States of America, [7]Dalhousie University, Halifax, Canada, [8]Feinstein Institutes for Medical Research, Northwell Health, New York, United States of America, [9]Mount Sinai School of Medicine, New York, United States of America, [10]Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, United States of America, [11]Cincinnati Children's Hospital Medical Center/University of Cincinnati, Cincinnati, United States of America, [12]King's College Hospital, London, United Kingdom, [13]University of Ferrara, Ferrara, Italy, [14]University Health Network, Toronto, Canada, [15]University of California, San Diego, United States of America, [16]Nova Scotia Health Authority, Halifax, Canada, [17]University of Toronto, Toronto, Canada, [18]Feinstein Institutes for Medical Research, Northwell Health, Manhasset, United States of America, [19]The Hospital for Sick Children, Neurosciences And Mental Health, Toronto, Canada, [20]Feinstein Institutes for Medical Research, Manhasset, United States of America, [21]Cincinnati Children's Hospital Medical Center, Cincinnati, United States of America, [22]Monash Health, Melbourne, Australia, [23]National Jewish Health, University of Colorado School of Medicine, Denver, United States of America, [24]Northwell Health, Manhasset, United States of America, [25]Centre for Musculoskeletal Research, Division of Musculoskeletal and Dermatological Sciences,

Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, United Kingdom, [26]Queen's University Belfast, Belfast, United Kingdom

Background/Purpose: Cognitive impairment (CI) is frequently observed in systemic lupus erythematosus (SLE) and negatively affects health-related quality of life. Despite increased research in this field, there remains a lack of multicentred studies and external validation of findings between centres. This abstract summarises the first international, multicentre meeting to discuss the harmonisation of research into CI in SLE. The aims of the meeting were to identify the current challenges in this field, knowledge gaps and opportunities to harmonise research across centres.

Methods: Thirty-seven interdisciplinary researchers (paediatric and adult rheumatologists, psychiatrists, psychologists, physicists, engineers) from 12 centres across six countries were invited. Researchers were selected based on having an established publication record in the field of CI in SLE. During the meeting two breakout groups were created, one focussed on clinical/psychological aspects and the other on neuroimaging. Key topics to discuss were prepared in advance, based on gaps in the current literature and areas that needed further understanding and consistency in research design. These included: core datasets needed for CI in SLE research, current cognitive measures used, weaknesses of these measures, differences between paediatric and adult CI, subjective versus objective CI, current neuroimaging in CI and gaps in the field.

Results: In terms of a core dataset there was a 'long-list' of factors discussed (Table 1). This was not a definitive list but a starting point for additional work required to determine priorities and core factors to consider in CI research. Instead of the American College of Rheumatology neuropsychological battery, identifying specific cognitive domains pertinent to patients with SLE was proposed. This proposed change would help overcome previous test limitations such as validation of tests in alternative languages and in a paediatric population. When considering the new domains, we also need to establish the purpose of the tool, for clinical or research. This setting would then also affect whether we need screening or in-depth measures. Measurements of both objective and subjective CI were considered important, as well as ecologically valid measures to capture cognitive performance in everyday life and measures of resilience. It was agreed that current CI measures account for some potential confounders (e.g. age and sex), but other important factors are overlooked, such as social determinants of health. The use of normative data can help with some confounders but regression-based norms maybe more useful. The neuroimaging breakout group identified ten acquisition methods in current use, with the majority collecting T1 structural, diffusion weighted imaging and resting state functional MRI. The group also identified 15 different types of software that are in use in the analysis stage (Table 2). Discussions included use of the "travelling head" methodology for

multi-centred studies, and the use of software algorithms in artificial intelligence to computationally harmonise some scans. Overall, in terms of harmonising imaging research across institutes four areas were targeted: scanner features and location, and participant, acquisition protocol, and analytic pipeline harmonisation.

Table 1: A list of some factors assessed when conducting CI in SLE research

- Depression
- Anxiety
- Fatigue
- Sleep disturbance/quality
- Pain
- Health-related quality of life
- SLE disease activity
- SLE disease damage
- SLE disease duration
- Co-morbidities (e.g. cardiovascular)
- Self-reported (subjective) cognitive symptoms
- Medication use: DMARDs, centrally acting medications
- Recreational drugs
- Attribution (TOMS Test of memory malingering)
- Construct measurement (cognitive function, dysfunction, impairment)
- Adverse childhood events – chronic stress – lifetime traumatic events
- Premorbid cognitive function, educational attainment
- Effort testing
- Economic – cost effective, health utility measures
- Specific to paediatric research:
    - Social risk within families
    - Primary language
    - Household education and income levels
    - Age at onset
- Serology, autoantibodies etc.
- Computer experience (if using computerized batteries)
- Behavioural factors – smoking, physical activity and obesity
- Personality

Table 2: Imaging data acquisition methods and software currently used by symposium attendees	
Acquisition methods	**Number**
T1 structural	5
DTI/DWI - Diffusion Tensor Imaging/Diffusion Weighted Imaging	5
rsfMRI - resting-state fMRI	5
Perfusion ASL/DCE-MRI - Arterial Spin Labelling/Dynamic Contrast Enhanced MRI	4
FLAIR - Fluid attenuated inversion recovery	3
PET - Positron Emission Tomography	2
MRS - Magnetic Resonance Spectroscopy	1
fMRI - functional MRI	1
7T structural	1
QSM - Quantitative Susceptibility Mapping	1
Analysis Software used	**Number**
FSL - Functional MRI of the Brain Software Library	4
SPM - Statistical Parametric Mapping	4
GIFT - Group ICA of fMRI Toolbox	3
Freesurfer	3
MatLab - Matrix Laboratory	2
ANTs - Advanced Normalization Tools	1
ItK-SNAP - brain imaging tool	1
Custom Python	1
Custom AI	1
Explore DTI	1
MRtrix - diffusion MRI analysis	1
ScAnVP - Scan Analysis and Visualisation Processor	1
CONN - functional connectivity toolbox	1
AFNI - Analysis of Functional NeuroImages	1
mrDiffusion - MR Diffusion Measurement	1

Conclusions: Studying CI in SLE is complex and is complicated further by its multifactorial nature and confounders. Minimising variation by harmonising research methods, especially clinical and imaging data acquisition and analysis across centres, is an important step to advancing knowledge of CI in the diverse population that is SLE patients. A wider international group will move forward with harmonisation efforts and development of a finalised core dataset. Acknowledgement: FAPESP grant 22/00597-6

O044 / #255

Topic: ***AS05 - CNS Lupus***

ABSTRACT CONCURRENT SESSION 07: COGNITION IMPAIRMENT IN SLE – RECENT ADVANCEMENT AND EMERGING RESEARCH
23-05-2025 1:40 PM - 2:40 PM

ELEVATED SERUM BRAIN INJURY MARKERS CORRELATE WITH DISEASE FEATURES AND INTERFERONS IN CHILDREN WITH SYSTEMIC LUPUS ERYTHEMATOSUS

Ganesh Ramanathan[1], Oscar Mwizerwa[1,2], Justine Ledochowski[1], Tala El Tal[1,3], Sarah Mossad[1,4], Ibrahim Mohamed[1], Joanna Law[1], Lawrence Ng[1,2], Paris Moaf[1], Asha Jeyanathan[1], Adrienne Davis[5], Ann Yeh[1,6], Linda Hiraki[7,8], Deborah Levy[2,9], Zahi Touma[10], Joan Wither[11], Busisiwe Zapparoli[1,4], Ashley Danguecan[12], Andrea Knight[1,2]
[1]SickKids Research Institute, Neurosciences And Mental Health Program, Toronto, Canada, [2]The Hospital for Sick Children, Rheumatology, Toronto, Canada, [3]Children's Hospital for Eastern Ontario, Pediatrics, Division Of Rheumatology And Dermatology, Ottawa, Canada, [4]The Hospital for Sick Children, Department Of Psychology, Toronto, Canada, [5]The Hospital for Sick Children, Emergency Medicine, Toronto, Canada, [6]The Hospital for Sick Children, Neurology, Toronto, Canada, [7]The Hospital for Sick Children, Genetics And Genome Biology, Toronto, Canada, [8]The Hospital for Sick Children,, Rheumatology, Toronto, Canada, [9]Child Health Evaluative Sciences, SickKids Research Institute, Toronto, Canada, [10]University of Toronto Lupus Clinic, Division of Rheumatology, Schroeder Arthritis Institute, Krembil Research Institute, University Health Network, Toronto, Canada, [11]Schroeder Arthritis Institute, Toronto Western Hospital, University of Toronto, Toronto, Canada, [12]The Hospital for Sick Children, Psychology, Toronto, Canada

Background/Purpose: Childhood-onset systemic lupus erythematosus (cSLE) involves interferon (IFN)-mediated inflammation emerging during the critical period of adolescent brain development. Neuropsychiatric lupus (NPSLE) manifests as syndromes like cognitive dysfunction, seizures, and psychiatric disorders, which negatively impact education, psychosocial functioning, and quality of life. While previous work indicates a type I IFN-α signature in cSLE, the levels of type II IFN-γ as well as the roles of both IFNs in the pathogenesis of brain inflammation have not been well established in literature. Moreover, clinicians face challenges diagnosing/treating brain inflammation in cSLE, due to suboptimal diagnostic tools. Neuronal/glial structural proteins may be useful biomarkers of brain injury in cSLE. We aimed to i) compare serum levels of brain injury markers and IFNs between children with cSLE and controls; and ii) investigate the relationship of brain injury markers to cSLE disease features and serum-IFN levels.

Methods: We utilized prospectively-collected cross-sectional data from cSLE participants (ages 12-17 years) recruited from the Lupus Clinic at a Canadian tertiary children's hospital from January 2020–December 2023, and age-, sex-matched healthy controls. Serum brain injury markers (serum neurofilament light (sNFL), glial fibrillary acidic protein (GFAP), Tau) were quantified using Simoa Human Neurology 4–Plex B assay; IFN-α and IFN-γ were also quantified with their respective Simoa assays (Quanterix, Billerca, MA, USA). Disease features included disease activity (SLEDAI-2K), damage (SLICC damage index, SDI > 0), glucocorticoid (GC) dose at study visit, and cumulative GC exposure (prednisone-equivalent). Wilcoxon rank sum test was used to compare markers/IFNs between cSLE and controls, and Spearman correlation tested associations.

Results: 56 cSLE participants (mean age = 15.1 ± 1.8 years, 86% female) and 43 controls (mean age = 15.1 ± 1.7 years, 81% female) were included. For cSLE, median disease duration was 22.6 months (IQR 12.5-43.9), median SLEDAI-2K was 2.5 (IQR 2.0-5.3), 9% had disease damage, 41% were using glucocorticoids at study visit, and median cumulative GC exposure was 1.9 grams (IQR 0.6-6.9). One patient had a NPSLE diagnosis. GFAP (114.0 vs 74.3 pg/mL) and Tau (3.57 vs 2.58 pg/mL) serum levels were significantly higher in cSLE compared to controls (Figure 1), as were serum IFN-α (0.278 vs 0.018 pg/mL) and IFN-γ (0.100 vs 0.068 pg/mL) levels (all $p < 0.05$). All brain injury markers had significant positive correlations with SLEDAI-2K and GC dose; sNFL and Tau associated with disease damage (Table 1). Higher levels of sNFL and GFAP correlated with IFN-α, while GFAP also associated with IFN-γ (Table 1). No correlations were found between Tau and IFNs.

Conclusions: Serum brain injury markers and type I and II IFNs were elevated in cSLE, with brain injury markers correlating with disease features, IFN-α, and IFN-γ. This suggests a link between IFN-mediated inflammation and neuronal/glial injury, and potential utility of sNFL, GFAP and Tau as diagnostic and monitoring biomarkers in cSLE. Also, these results indicate IFNs are potential therapeutic targets in cSLE. Future studies will explore relationships between brain injury markers and IFNs in larger cSLE cohorts over time.

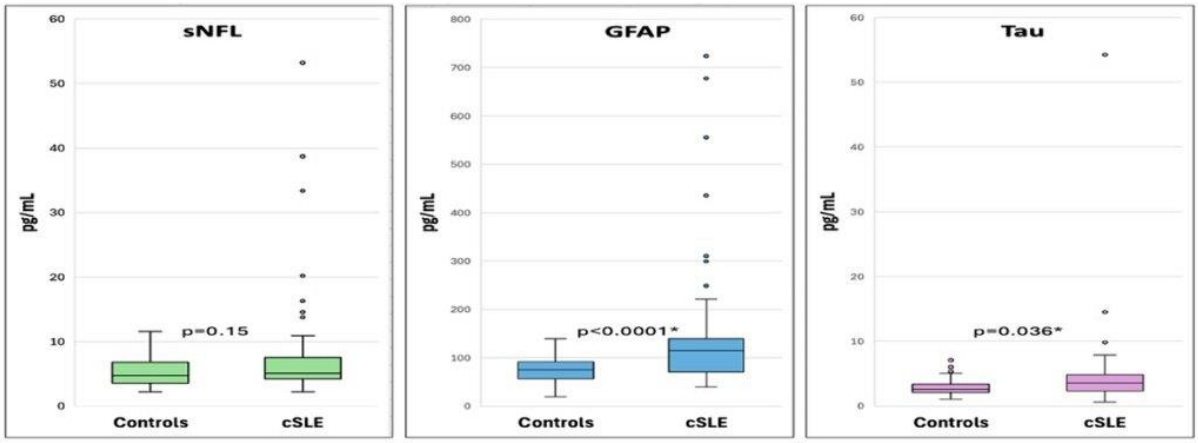


Figure 1: Boxplots showing group differences in serum brain injury marker levels between cSLE and controls. GFAP and Tau were significantly elevated in cSLE group (Wilcoxon rank sum test, $p < 0.05$), with outliers also observed across all brain injury markers for cSLE.

Table 1: Relationship between Brain Injury Markers, Disease Characteristics, and Interferons in cSLE (n=56)

	SLEDAI-2K at Study Visit	SDI	Current GC Dose	Cumulative GC Exposure	IFN-α	IFN-γ
sNFL	r = 0.30 **p = 0.027**	r = 0.27 **p = 0.045**	r = 0.30 **p = 0.025**	r = 0.13 p = 0.350	r = 0.30 **p = 0.022**	r = 0.24 p = 0.069
GFAP	r = 0.30 **p = 0.025**	r = 0.22 p = 0.097	r = 0.30 **p = 0.027**	r = -0.14 p = 0.316	r = 0.27 **p = 0.048**	r = 0.28 **p = 0.034**
Tau	r = 0.40 **p = 0.002**	r = 0.33 **p = 0.014**	r = 0.27 **p = 0.045**	r = 0.15 p = 0.273	r = 0.05 p = 0.703	r = 0.03 p = 0.798

Shown are Spearman correlations analyzing relationships between serum brain injury markers, cSLE disease features, and serum-IFN levels. Statistically significant correlations are bolded ($p<0.05$).

O045 / #659

Topic: ***AS05 - CNS Lupus***

ABSTRACT CONCURRENT SESSION 07: COGNITION IMPAIRMENT IN SLE – RECENT ADVANCEMENT AND EMERGING RESEARCH
23-05-2025 1:40 PM - 2:40 PM

SERUM S100A8/A9, MMP-9 AND IL-6 ARE ASSOCIATED WITH IMPAIRMENT IN EXECUTIVE FUNCTION, SIMPLE ATTENTION AND PROCESSING SPEED IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

Emma Neary[1], Carolina Munoz-Grajales[2], Joan Wither[3], Juan Pablo Diaz Martinez[2], Michelle Barraclough[4], Kathleen Bingham[2], Roberta Kretzmann[2], Carmela Tartaglia[2], Lesley Ruttan[2], May Choi[5], Simone Appenzeller[6], Sherief Marzouk[2], Dennisse Bonilla[3], Patti Katz[7], Dorcas Beaton[2], Robin Green[2], Laura Whittall-Garcia[3], Dafna D Gladman[8], Zahi Touma[8]
[1]McGill University, Montreal, Canada, [2]University Health Network, Toronto, Canada, [3]Schroeder Arthritis Institute, Toronto Western Hospital, University of Toronto, Toronto, Canada, [4]NIHR Manchester Biomedical Research Centre, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, United Kingdom, [5]University of Calgary, Medicine, Calgary, Canada, [6]University of Campinas, Campinas, Brazil, [7]University of California San Francisco, San Francisco, United States of America, [8]University of Toronto Lupus Clinic, Division of Rheumatology, Schroeder Arthritis Institute, Krembil Research Institute, University Health Network, Toronto, Canada

Background/Purpose: Cognitive impairment (CI) is a common manifestation in patients with systemic lupus erythematosus (SLE). Despite its impact on patient quality of life, treatments remain limited as its pathogenesis is poorly understood. The Automated Neuropsychological Assessment Metrics (ANAM) has superior patient acceptability and feasibility in ambulatory settings compared to the American College of Rheumatology Neuropsychological Battery (ACR-NB) [gold-standard test] and is validated in screening for CI in SLE. Data from our laboratory have revealed that serum S100A8/A9 and MMP-9 are associated with CI measured by the ACR-NB. However, the relationship between these serum analytes, ANAM subtests and CI has not been elucidated. We therefore aimed to determine if serum analytes are associated with CI measured by the ANAM.

Methods: We cross-sectionally analyzed the data of 327 adults aged 18-65 who were followed longitudinally between January 2016 and October 2019 at a single SLE center. All participants fulfilled the 2019 EULAR/ACR SLE classification criteria. Cognitive function was measured using ANAM throughput scores, and serum levels of 9 analytes (IL-10, IL-6, IFN-γ, TNF-α, TWEAK, S100B, S100A8/A9, NGAL and MMP-9) were measured

using ELISA. The K-means clustering algorithm was used to cluster the patient data, and the Principal Component Analysis (PCA) characterized the clusters. The silhouette coefficient (s) was calculated for 2 to 15 clusters to determine the optimal number of clusters.

Results: PCA identified two principal components explaining 36.2% of the variance in ANAM throughputs and serum analytes. The first component (26.7% of the variance) was correlated with ANAM throughputs, with the strongest contribution from procedural reaction time. The second component (9.44% of the variance) was correlated with serum analyte measurements, with the strongest contribution from TNF-alpha. [Figure 1] The highest silhouette value was found for 2 (s = 0.177) and 3 (s = 0.176) clusters. Only 4% of patients were classified in the 3 cluster model, so a 2 cluster model was selected. Cluster 1 had low throughput scores representing CI, and Cluster 2 had higher throughput scores representing no CI. A significant difference was observed in mean serum S100A8/A9 (SMD = 0.362), MMP-9 (SMD = 0.178) and IL-6 (SMD = 0.311) between the clusters, reflected by their correlation with the first principal component. [Figure 2] Serum levels of S100A8/A9, MMP-9 and IL-6 had a strongly negative correlation between the Go No Go and Running Memory throughputs.

Conclusions: Serum S100A8/A9, MMP-9, and IL-6 are associated with CI in SLE as measured by the ANAM. Patient clusters with elevated serum S100A8/A9, MMP-9, and IL-6 had strongly negative associations with throughputs representing impairment in executive function, simple attention and processing speed. Further studies are needed to uncover mechanistic relationships between these analytes and CI in SLE, and whether they may represent valuable therapeutic targets for further exploration. **Figure 1: Correlation matrix for individual ANAM throughputs and serum analyte levels**

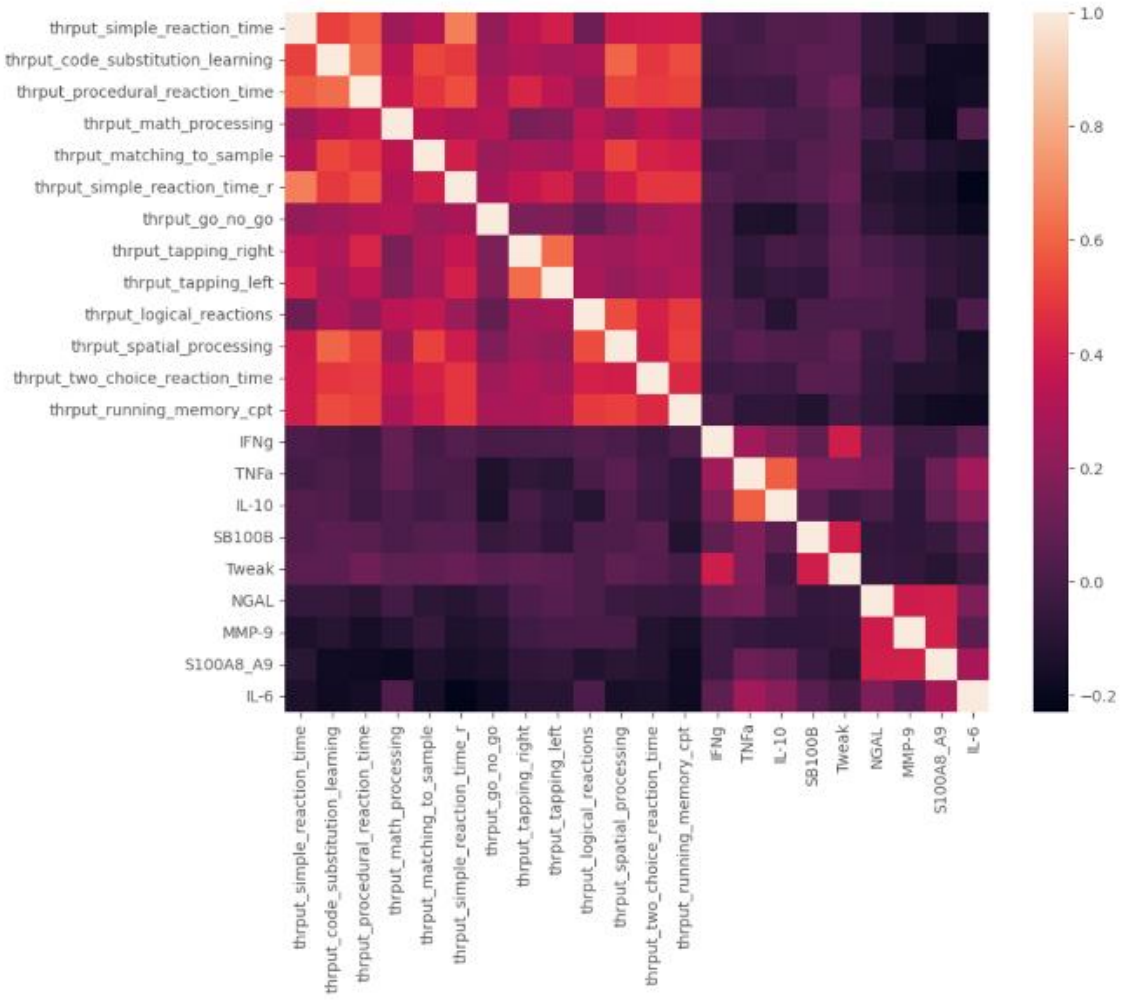


Figure 1 legend

- Lighter colors = higher standardized mean differences (SMD), representing greater differences between the two clusters.
- Darker colors = lower standardized mean differences (SMD), representing lesser differences between the two clusters.

Figure 2: Biplot of the first 2 principal components, with 2 clusters and association with analytes

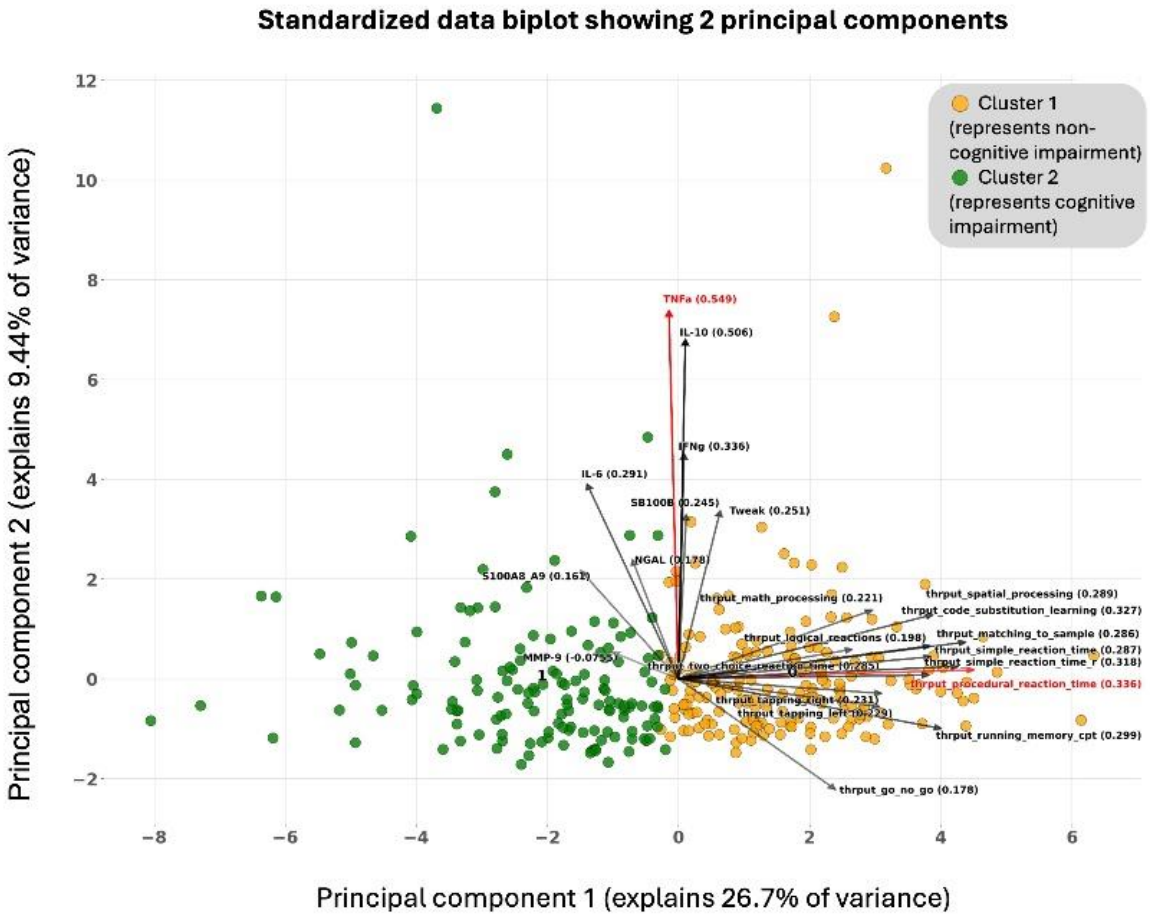


Figure 2 interpretation: The biplot displays the clusters projected on the first two principal components, which explains 36.2% of the variance in ANAM throughputs and serum analytes. Axis x represents the first component (explains 26.7% of the variance), which correlates with ANAM throughputs. Axis y represents the second component (explains 9.44% of the variance), which correlates with serum analyte measurements. The arrows represent the variables, and their direction indicates the relationship between the variables and the clusters. The length of the arrows indicates the strength of the relationship between the variable it represents and the cognitive dimensions.

O046 / #556

Topic: ***AS02 - Animal Models***

ABSTRACT CONCURRENT SESSION 07: COGNITION IMPAIRMENT IN SLE – RECENT ADVANCEMENT AND EMERGING RESEARCH
23-05-2025 1:40 PM - 2:40 PM

EXPANSION OF BRAIN T CELL SUBSETS OUTSIDE OF THE CHOROID PLEXUS IN MOUSE MODELS OF NEUROPSYCHIATRIC LUPUS

Minjung Kim, Cecilia Stumpf, Mohammad Khan, Vanessa Rodriguez, Tyler Therron, Deborah Winter, Carla Cuda
Northwestern University, Medicine-rheumatology, Chicago, United States of America

Background/Purpose: Unclear mechanisms underlying diffuse NPSLE (psychosis, anxiety disorder, cognitive dysfunction) may lead to the devastating impact of this disease on patients' health-related quality-of-life, representing a major unmet need in the field. In prior work, systemic depletion of CD4+ T cells ameliorated both systemic disease and behavior deficits in SLE- and NPSLE-prone MRL/lpr mice by reducing choroid plexus-infiltrating CD4+ T cells as well as indirectly preventing CD8+ T cell infiltration. Further, increased markers of exhaustion were identified in choroid plexus-infiltrating CD8+ T cells of MRL/lpr mice. However, NPSLE is heterogeneous in its presentation; choroid plexus infiltrate is not a fully penetrant hallmark of human NPSLE or other disease models. Thus, it is critical to elucidate the contribution of T cell subsets outside of the choroid plexus to NPSLE.

Methods: Perfused brains of female SLE- and NPSLE-prone CReCOM (8 mo old; n=4-11) and B6.*Sle1Sle2Sle3* (TC; 2 and 8 mo old; n=3-4) mice, and respective control strains, were extracted after intravenous CD45 labeling to exclude remaining circulating immune cells, dural meninges were removed, and cells were analyzed by flow cytometry. Young female CD45.1 (Jackson 033076) and TC mice were used to generate reciprocal head-shielded BM chimeric mice with busulfan treatment to clear remaining BM (CD45.1 BM::CD45.1; TC BM::CD45.1; CD45.1 BM::TC; TC BM::TC). Mice underwent behavioral tasks 10 weeks post-transfer. Live CD45+cells were FACSorted from pooled cell suspensions (n=3/group to account for biological variability) for cellular indexing of transcriptomes and epitopes by sequencing (CITE-seq; 10X Genomics 3' v3.1). Data from CD45.1 BM::CD45.1 and TC BM::TC chimeras were analyzed in R using the Seurat package. Post-filtering, ~10K cells/chimera were maintained.

Results: Extravascular CD8+ T cells are significantly increased in the brains of CReCOM and TC mice (8 mo old) compared to their respective control strains. Further, this increase is evident at 2 months of age in TC mice. Evaluation of extravascular T cells by CITE-seq in CD45.1 BM::CD45.1 and TC BM::TC chimeric mice was carried out to mimic

that of control and NPSLE-prone strains, respectively, in systemic disease and behavioral phenotypes. Similar to data from the kidney and choroid plexus of MRL/lpr mice, we show expansion of an exhausted (*Pdcd1, Eomes, Tox*) CD8+ T cell subset. We also identify an expanded IL-17-producing gamma-delta T cell subset previously unassociated with NPSLE-like disease but implicated in neuro-autoimmune and -degenerative diseases (multiple sclerosis, Alzheimer's disease). As CReCOM and TC mice do not present with the characteristic choroid plexus infiltrate of the MRL/lpr strain, these subsets mediate their activity in the brain parenchyma or non-dural meninges.

Conclusions: We find expansion of an exhausted CD8+ T cell subset in the brain of NPSLE-prone mice that may transition from a highly activated T cell state. An IL-17-producing gamma-delta T cell subset not previously associated with NPSLE was also expanded. Future studies will interrogate these specialized T cell subsets for their location of action to further uncover their role of in NPSLE-like disease.

O046a / #565

Topic: ***AS01 - Adaptive Immunity***

ABSTRACT CONCURRENT SESSION 07: COGNITION IMPAIRMENT IN SLE – RECENT ADVANCEMENT AND EMERGING RESEARCH
23-05-2025 1:40 PM - 2:40 PM

COVID-19 AND POST COVID-19 AND THE EMERGENCE OF SLE AND EXACERBATIONS

Yehuda Shoenfeld
Sheba Medical centre, Autoimmune Centre, Ramat gan, Israel

Background/Purpose: Covid-19 virus is an autoimmune virus and more notorious than EBV. It induces autoimmune diseases by **hyper-stimulation** combined with induction of autoimmune disease by **molecular mimicry**. There are many autoimmune conditions which have emerged following the COVID 19 infection. One of them is **SLE**. We will summarize the various publications discussing **de novo** eruption of SLE as well as induction of exacerbation.

Methods: We assume the possibility of an alternative course of COVID-19, which develops in genetically predisposed individuals with a stronger immune response, in which it predominantly affects the cells of the nervous system, possibly with the presence of an **autoimmune component**, which might have similarity with chronic fatigue syndrome or autoimmune **dysautonomia**.

Results: We will discuss all the autoimmune ramifications of the virus, the CFS / fibromyalgia / post Covid syndrome. (1-7) and their association with **SLE.**

Conclusions: The detection of novel autoantibodies to the **autonomic nervous system receptors** will explain the pathogenic mechanism of many of the new complaints. References 1. Yehuda Shoenfeld, et al/ Complex syndromes of chronic pain, fatigue and cognitive impairment linked to autoimmune dysautonomia and small fiber neuropathy. Clinical Immunology 2020; 214: 108384. 2. Otavio Cabral-Marques Gilad Halpert, Harry Heidecke…Avi Z. Rosenberg 24, Gabriela Riemekasten 13,25✉ & Yehuda Shoenfeld .Autoantibodies targeting GPCRs and RAS-relate molecules associate with COVID19 Severity. Nature Commun 2022 3. Arad Dotan, Yehuda Shoenfeld. Post-COVID syndrome: the aftershock of SARS-CoV-2. InternationalJ Infectious Diseases 2022; 114: 233–235. doi: 10.1016/j.ijid.2021.11.020. PMID: 34785367. 4 Luis J. Jara, …, Yehuda Shoenfeld. Autoimmune post-COVID vaccine syndromes: does the spectrum of autoimmune/ inflammatory syndrome expand? Clinical Rheumatology 2022; 41:1603–1609. https://doi.org/10.1007/s10067-022-06149-45. Michael Ehrenfeld, …, Howard Amital, Yehuda Shoenfeld. COVID-19 and autoimmunity. Autoimmunity Reviews 2020; 19:

102597.https://doi.org/10.1016/j.autrev.2020.102597 6. Carlo Perricone, Elena Bartoloni, Roberto Bursi, Giacomo Cafaro, Giacomo Maria Guidelli, Yehuda Shoenfeld, Roberto Gerli. COVID-19 as part of the hyperferritinemic syndromes: The role of iron depletion therapy. Immunologic Research (2020) 68:213–224. https://doi.org/10.1007/s12026-020-09145-5 7 Gilad Halpert, Yehuda Shoenfeld. SARS-CoV-2, the autoimmune virus. Autoimmunity Reviews 2020; 19: 102695 8. Rogue antibodies could be driving severe COVID-19. (Interview in "Nature" with Yehuda Shoenfeld). Nature 2021; Published: 4 February 2021. pp: 29-31. https://www.nature.com/articles/d41586-021-00149-1 *doi: https://doi.org/10.1038/d41586-021-00149-1* 9 Arad Dotan, Sylviane Muller, Darja Kanduc, Paula David, Gilad Halpert, Yehuda Shoenfeld. The SARS-CoV-2 as an instrumental trigger of autoimmunity. Autoimmunity Reviews 2021; 20: 102792. pp. 1-9. https://doi.org/10.1016/j.autrev.2021.102792. 10. Abdulla Watad , ..Yehuda Shoenfeld, Howard Amital, Dennis McGonagle. Immune-Mediated Disease Flares or New-Onset Disease in 27 Subjects Following mRNA/DNA SARS-CoV-2 Vaccination. Vaccines 2021; 9: 435. (23 pp). https://doi.org/10.3390/vaccines9050435

O047 / #343

Topic: ***AS03 - Antiphospholipid Syndrome***

ABSTRACT CONCURRENT SESSION 08: RECENT ADVANCES IN LUPUS BIOMARKERS
23-05-2025 1:40 PM - 2:40 PM

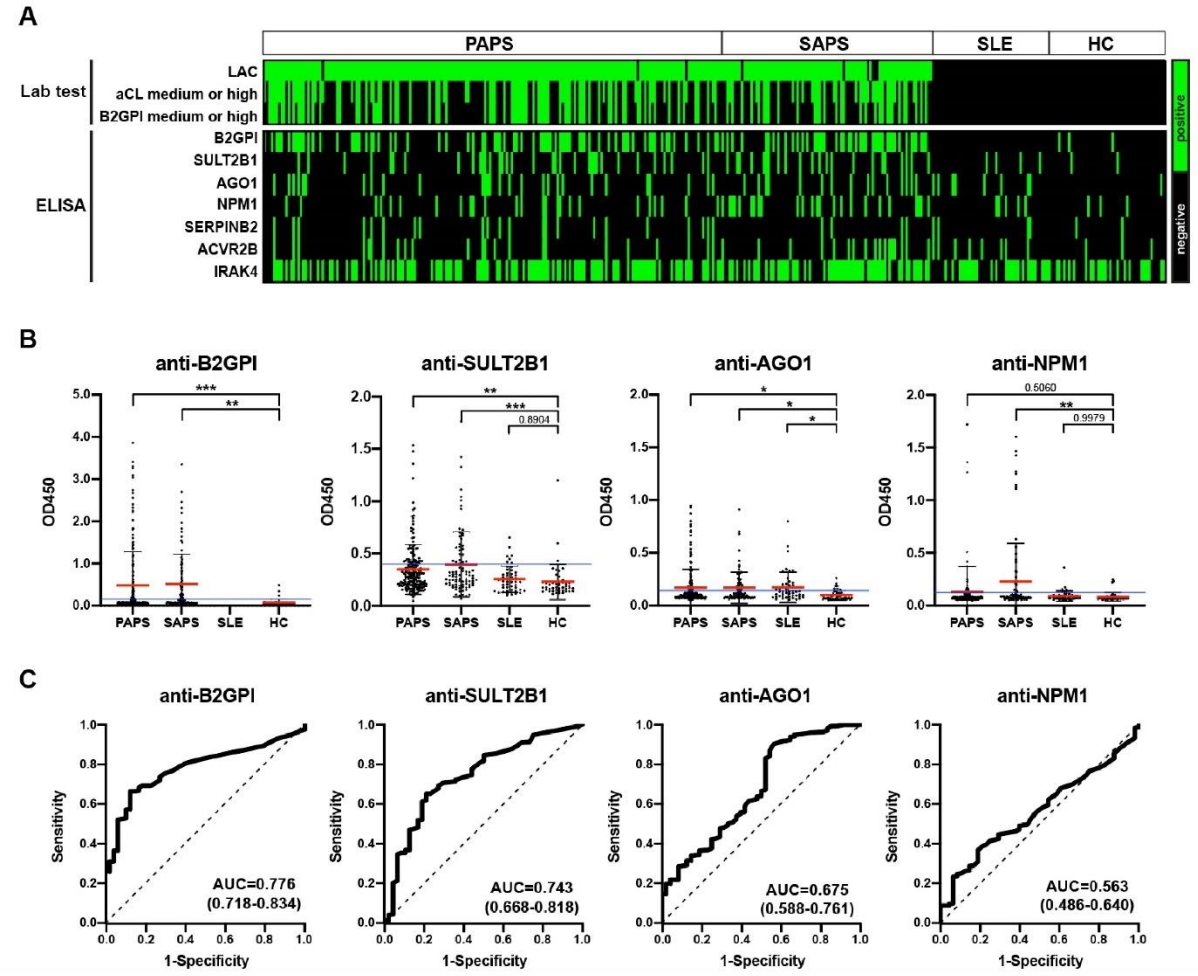
NOVEL AUTOANTIBODIES IDENTIFIED IN THE ANTIPHOSPHOLIPID SYNDROME

Shikai Hu, Yangzhong Zhou, Menghua Cai, Mengtao Li, Jiuliang Zhao
Peking Union Medical College Hospital, Beijing, China

Background/Purpose: The antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by arterial, venous, or microvascular thrombosis, recurrent pregnancy morbidity, or non-thrombotic manifestations in the setting of persistent antiphospholipid antibodies (aPL), namely anti-β2 glycoprotein-I antibody (aβ2GPI), anticardiolipin antibody (aCL), and lupus anticoagulant (LAC). Around one-third of the APS patients had an isolated LAC positivity lacking aβ2GPI and aCL. This study aimed to identify novel autoantibodies in APS using protein microarray technology.

Methods: Sera from APS patients, disease controls (DCs), and healthy controls (HCs) were applied to the HuProt™ Human Proteome Microarray v4.0 for the discovery of novel autoantibodies. Candidate autoantibodies were then validated using ELISA in an additional 372 sera samples, comprising 189 primary APS patients, 87 secondary APS patients, 48 SLE patients, and 48 HCs.

Results: During the discovery phase, HuProt microarrays were incubated with serum samples (5:1 mixture) from APS patients, DCs, and HCs to identify APS-associated autoantigens. Approximately twenty autoantigens were identified for subsequent validation. These potential autoantigens include proteins involved in or associated with ubiquitination and deubiquitination (UBE3A, ATXN3), proteasome (PSME3), microtubule (MAP9), vesicular transport (ASAP2), ribosome (NPM1, RPLP2), amino acid modification (PRMT7), DNA and RNA (RBM38, IRX2, AGO1), inflammation (WDR54, IRAK4, ACVR2B, N4BP1, MX1), metabolism (ACSBG1, SULT2B1, HK1, GLOD4), coagulation factor (SERPINB2), and others. In the validation phase, six proteins (SULT2B1, NPM1, AGO1, SERPINB2, ACVR2B, IRAK4) were selected and validated using ELISA. Anti-SULT2B1 and anti-AGO1 autoantibodies were significantly higher in primary APS patients. Anti-SULT2B1, anti-AGO1, and anti-NPM1 were also significantly higher in secondary APS patients. Anti-NPM1 positive patients exhibited a significantly higher incidence of SLE (50.9% vs 33.7%, p=0.013), cardiac valve involvement (16.3% vs 6.1%, p=0.031), and triple positivity (53.1% vs 33.5%, p=0.010) compared to anti-NPM1 negative patients. Validation of other autoantibodies is ongoing.



Conclusions: We identified novel autoantibodies targeting proteins involved in a broad range of biological processes in APS. Anti-SULT2B1, anti-AGO1, and anti-NPM1 autoantibodies were identified in APS patients, demonstrating diagnostic and clinical value. Further validation of additional autoantibodies in larger APS cohorts is ongoing.

O048 / #626

Topic: ***AS15 - Lupus Nephritis-Clinical***

ABSTRACT CONCURRENT SESSION 08: RECENT ADVANCES IN LUPUS BIOMARKERS
23-05-2025 1:40 PM - 2:40 PM

UTILITY OF URINARY BIOMARKERS TO PREDICT LONG-TERM RENAL OUTCOMES IN LUPUS NEPHRITIS

Laura Whittall-Garcia[1], Ryan Baker[1], Michael Kim[2], Dennisse Bonilla[1], Murray Urowitz[3], Dafna D Gladman[1], Zahi Touma[1], Joan Wither[1]
[1]University of Toronto Lupus Clinic, Toronto, Canada, [2]Schroeder Arthritis Institute, Krembil Research Institute, University Health Network, Toronto, Ontario, Canada, Toronto, Canada, [3]Self employed, Toronto, Canada

Background/Purpose: Lupus nephritis (LN) affects up to 50% of patients with lupus, of whom 40% will experience a subsequent renal flare, and up to 20% will progress to end-stage renal disease. Repeat kidney biopsies (KB) performed 2 years after the last LN flare have been shown to predict subsequent renal flares and renal dysfunction. In this study, we assessed whether five urinary biomarkers (UB), including CD163, MCP-1, Adiponectin, sVCAM-1 and PF4 measured 2 years after a LN flare, predict long-term renal outcomes.

Methods: Patients who had a LN flare and stored urine 24±3 months after the LN flare were included in the study. The 5 UB levels were measured by ELISA 24±3 months after the LN flare. Examined renal outcomes: 1) Time to a subsequent LN flare (increase in proteinuria of at least 1000 mg/day if the baseline was <500 mg/day or doubling of proteinuria if the baseline was ≥500 mg/day, prompting a change in therapy) and 2) time to 30% decline in eGFR, after their 2-year urinary sample collection.

Results: 69 patients with LN were included. The median (IQR) follow-up time after their 2-year urinary sample collection was 129 (97.5-150) months. 50 patients achieved proteinuria of ≤700mg at 2 years after the LN flare. This sub-cohort of patients had significantly lower UB levels 2 years after the LN flare compared to patients who persisted with proteinuria >700mg (Figure 1). In this sub-cohort of patients, 27 (54%) experienced a subsequent LN flare with a median time to flare (IQR) of 3.5 (1.67-6.87) years, and 10 (20%) had a 30% decline in eGFR at a median time of 4.38 (3.73-5.33) years after their 2-year urinary sample collection. Elevated levels of MCP-1 (HR 1.13 (1.01-1.27), p=0.03) and CD163 (HR 1.48 (1.15-1.90), p=0.002) predicted a subsequent LN flare. While CD163 (HR 1.31 (1.10-1.57), p=0.002), Adiponectin (HR 1.53 (1.22-1.91), p=0.0002), sVCAM-1 (HR 1.11 (1.03-1.21), p=0.006), and PF4 (HR 1.14 (1.04-1.25), p=0.003) predicted a 30% decline in eGFR (Table 1).

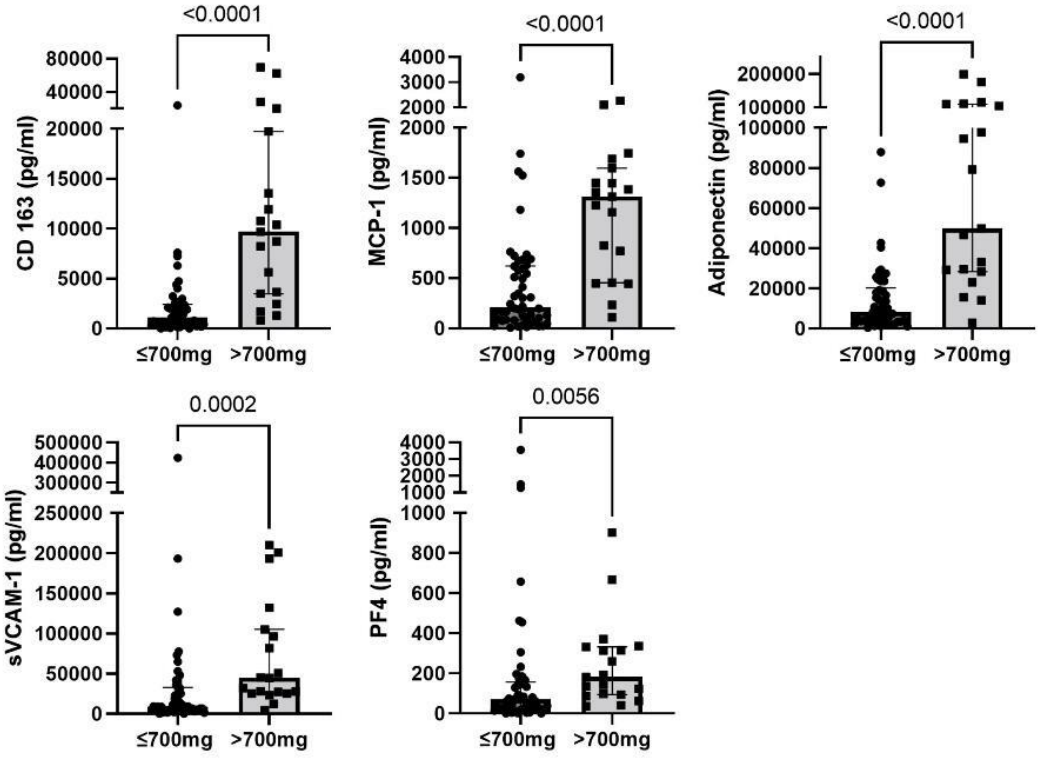


Figure 1. UB were significantly higher in patients who did not achieve an uPCR ≤700mg (n=19) at 24±3 months after the LN flare as compared to those who did (n=50). Symbols represent the determination from a single individual, columns the median and the bars IQR.

Table 1. Multivariable Cox Regression analysis. Predictors of adverse renal outcomes (Sub-cohort of patients who achieved a proteinuria of ≤700mg at 24±3 months after the LN flare, N=50)

	Subsequent LN flare*		**30% decline in eGFR****	
Variables at the time of urine collection [a]	**Hazard Ratio (95% CI)**	**P value**	**Hazard Ratio (95% CI)**	**P value**
CD163 (pg/ml)	1.48 (1.15-1.90)	**0.002**	1.31 (1.10-1.57)	**0.002**
MCP-1 (pg/ml)	1.13 (1.01-1.27)	**0.03**	1.08 (0.93-1.27)	0.28
Adiponectin (pg/ml)	1.09 (0.92-1.29)	0.30	1.53 (1.22-1.91)	**0.0002**
sVCAM-1 (pg/ml)	1.003 (0.99-1.01)	0.55	1.11 (1.03-1.21)	**0.006**
PF4 (pg/ml)	0.97 (0.88-1.07)	0.55	1.14 (1.04-1.25)	**0.003**
Proteinuria (mg)	1.52 (0.98-2.34)	0.052	1.37 (0.67-2.80)	0.38

Serum albumin (g/L)	0.85 (0.71-1.02)	0.09	0.85 (0.65-1.11)	0.22
Serum creatinine (umol/L)	1.23 (0.67-2.27)	0.49	1.99 (0.86-4.19)	0.10

*Cox regression analysis adjusted for age and ethnicity and ** adjusted for age. [a] HR expressed are for every increase in: 1000pg/ml of CD163, 200pg/ml of MCP-1, 8000pg/ml of Adiponectin, 8000pg/ml of sVCAM-1, 100pg/ml of PF4, 200mg of proteinuria, 2g/L of serum albumin, 30 µmol/L of serum creatinine.

Conclusions: UB measured 2 years after an LN flare predicted long-term renal outcomes.

O049 / #570

Topic: ***AS04 - Biomarkers***

ABSTRACT CONCURRENT SESSION 08: RECENT ADVANCES IN LUPUS BIOMARKERS
23-05-2025 1:40 PM - 2:40 PM

METABOLITES ARE ASSOCIATED WITH FLARE REMISSION AND DNA METHYLATION CHANGES IN SYSTEMIC LUPUS ERYTHEMATOSUS

Mary Horton[1], Dylan Johnson[2], Kirsten Overdahl[2], Joanne Nititham[1], Kimberly Taylor[3], Patti Katz[3], Chun Jimmie Ye[3], Jinoos Yazdany[3], Maria Dall'Era[3], Lisa Barcellos[4], Jian-Lang Li[2], Alan Jarmusch[2], Lindsey Criswell[1], Cristina Lanata[1]
[1]NIH/NHGRI, Bethesda, United States of America, [2]NIH/NIEHS, Durham, United States of America, [3]University of California, San Francisco, San Francisco, United States of America, [4]University of California, Berkeley, Berkeley, United States of America

Background/Purpose: Recently, interest has increased in the role of metabolites and metabolic pathways in autoimmunity and SLE. Evidence suggests that immune cells are influenced by metabolic programs. Several studies identified metabolites with different levels in SLE cases compared to controls. It is unknown whether metabolite levels are associated with SLE disease activity or are correlated with other biomarkers of SLE disease activity such as DNA methylation. Metabolites, and their correlations with other markers, might serve as indicators of immune cell function and improve our ability to successfully treat patients. Using a cohort of SLE patients recruited during a flare and followed-up over time, we aimed to identify whether changes in metabolites were associated with flare remission and whether these changes were correlated with changes in DNA methylation.

Methods: Forty multi-ethnic SLE patients were recruited during a rheumatologist-confirmed flare and returned to the clinic approximately three months later. At both visits, we obtained whole blood and generated untargeted metabolomics data from plasma (LC-QTOF) and DNA methylation profiles (Illumina EPIC array). Clinical data, including SLEDAI SELENA and medications, were collected at each visit. Remission was defined as SLEDAI=0 at the follow-up visit. We identified metabolites whose changes over time were associated with remission status, after adjusting for follow-up time and medications, using linear regression models. Previously in this study sample and using a similar statistical approach, we identified 291 DNA methylation sites whose changes over time were associated with remission. Significant metabolite changes (FDR q<0.05) were tested for their association with DNA methylation changes at these 291 sites using correlation coefficients.

Results: Sixteen SLE patients were in remission at the follow-up visit. Remitters and non-remitters did not differ significantly by race, ethnicity, age, disease activity or

symptoms at the baseline flare, or medications. We identified nine metabolite changes associated with remission status. These included oleic acid (P= 5.49x10^{-8}) and two isomers of adenine (P= 3.77x10^{-5}, each). For non-remitters, these metabolite levels changed very little between visits. For remitters, four metabolites increased while five decreased between visits. We identified 57 significantly correlated metabolite-DNA methylation pairs. This included a strong correlation between oleic acid and a DNA methylation site within the body of *EBF1*, an interferon response gene and key transcription factor of B-cell specification (correlation = -0.79, p=1.1x10^{-7}). We also identified a strong correlation between adenine and a DNA methylation site within the body of *IL12B*, another interferon response gene which encodes a cytokine that acts on T and natural killer cells (correlation = 0.70, p=1.30x10^{-6}).

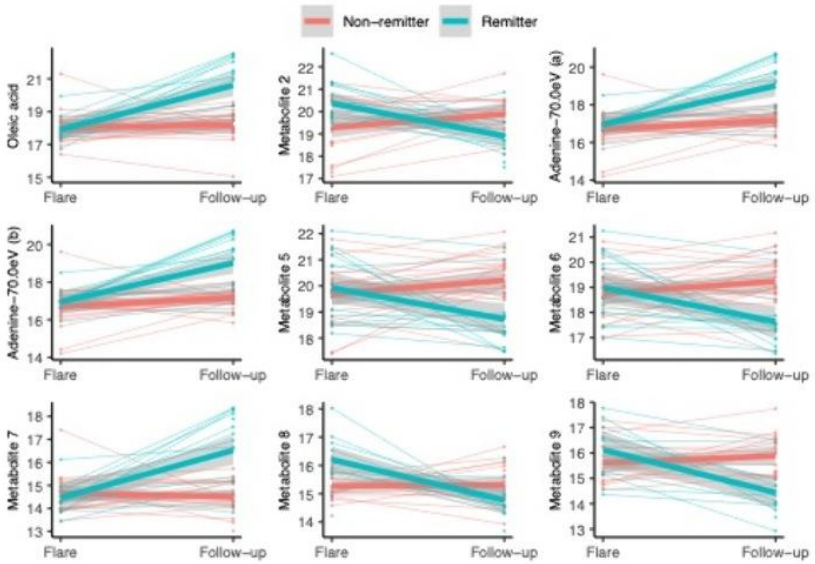


Figure 1. Nine metabolites had levels that changed between flare and follow-up visits differently by remission status (FDR q<0.05). Colors represented patient's remission status. Bold line represented mean change in metabolite by remission status.

Conclusions: Current treatments do not adequately prevent SLE flares or disease-related organ damage. Understanding the biological markers and pathways associated with remission after a flare might improve our ability to successfully treat patients. Our results showed that changes in several metabolites, including oleic acid and adenine, were associated with remission status and were correlated with changes in DNA methylation at SLE-relevant loci. These might be promising targets for future therapeutics and help us understand the underlying biology of SLE.

Acknowledgements: This work was funded in part by U01DP005120 CDC.

O050 / #258

Topic: ***AS20 - Precision Medicine***

ABSTRACT CONCURRENT SESSION 08: RECENT ADVANCES IN LUPUS BIOMARKERS
23-05-2025 1:40 PM - 2:40 PM

NOVEL IGG AND IGA AUTOANTIBODIES IN TWO INDEPENDENT COHORTS ASSOCIATE WITH GLOBAL AND ORGAN-SPECIFIC DISEASE ACTIVITY IN SYSTEMIC LUPUS ERYTHEMATOSUS: IMPLICATIONS FOR ANTI-LIN28A AND ANTI-IRF5

Julius Lindblom[1], Denis Lagutkin[1], Natalia Sherina[1], Helena Idborg[1], Lorenzo Beretta[2], Maria Orietta Borghi[3], Precisesads Clinical Consortium[4], Janique M Peyper[5], Guillermo Barturen[4], Per-Johan Jakobsson[1], Marta Alarcón-Riquelme[4], Dionysis Nikolopoulos[1], Ioannis Parodis[1,6]
[1]Karolinska Institutet and Karolinska University Hospital, Division Of Rheumatology, Department Of Medicine, Solna, Stockholm, Sweden, [2]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Referral Center For Systemic Autoimmune Diseases, Milan, Italy, [3]Università Degli Studi di Milano, Department Of Clinical Sciences And Community Health, Milan, Italy, [4]Centre for Genomics and Oncological Research, University of Granada, Granada, Spain, [5]Sengenics Corporation Pte Ltd, Singapore, Singapore, [6]Örebro University, Department Of Rheumatology, Faculty Of Medicine And Health, Örebro, Sweden

Background/Purpose: Autoantibodies are a hallmark of systemic lupus erythematosus (SLE), but among a multitude of autoantigen specificities, few are mapped and used in routine clinical practice. Autoantibodies currently used for surveillance, such as anti-dsDNA, show only modest associations with SLE disease activity. The aim of this study was to identify and validate novel autoantibodies that reflect global and organ-specific disease activity in systemic lupus erythematosus (SLE).

Methods: Serum samples were screened for IgG and IgA seroreactivity against 1609 protein autoantigens using an immunome microarray (Sengenics). We determined differentially abundant autoantibodies (daAAbs) in SLE patients versus healthy controls within a discovery (n=199 versus n=111) and an independent validation cohort (n=30 versus n=84) from the European PRECISESADS project (NTC02890121). Validated daAAbs were analysed in relation to global and organ-specific disease activity using linear and logistic regression, along with daAAb target pathway enrichment analysis.

Results: We validated 89 IgG and 66 IgA daAAbs. IgG anti-LIN28A, IgG anti-HMGN5, and both isotypes for anti-IRF5 and anti-TGIF1 were associated with a SLE Disease Activity Index 2000 (SLEDAI-2K) score ≥10, negatively associated with Lupus Low Disease Activity State (LLDAS), and highly prevalent in patient subgroups with active disease across organ manifestations. IgG anti-LIN28A levels exceeded the cut-off for positivity

in 53% of patients with CNS involvement, a prevalence higher than that observed for anti-dsDNA (20%), and 47% of patients with renal activity. A cluster of IgG and IgA daAAbs against RNA-binding proteins, including anti-LIN28A, was predominantly represented in patients with CNS activity. IgA anti-FOSL2 was associated with musculoskeletal activity. Enriched pathways related to DNA binding and repair exhibited considerable overlap across organ systems.

Conclusions: This study identified and validated novel IgG and IgA autoantibodies. Among those, IgG anti-LIN28A, IgG anti-HMGN5, and both isotypes for anti-IRF5 and anti-TGIF1 were associated with high disease activity and were highly prevalent in subgroups of patients with active disease across organ manifestations. IgG anti-LIN28A levels exceeded the cut-off for positivity in more than half of the patients with CNS involvement, a prevalence higher than that observed for the routine clinical marker anti-dsDNA, and almost half of the patients with renal activity. Additionally, IgG and IgA LIN28A formed autoantibody clusters predominantly represented in patients with CNS activity. The findings of IgA seroreactivity are novel and point to the importance of mucosal immunity in SLE, while the overall findings have direct implications for the early identification of patients with active or evolving disease, and for timely and informed therapeutic intervention.

O051 / #519

Topic: ***AS04 - Biomarkers***

ABSTRACT CONCURRENT SESSION 08: RECENT ADVANCES IN LUPUS BIOMARKERS
23-05-2025 1:40 PM - 2:40 PM

IMPROVEMENT OF THROMBOSIS-RELEVANT BIOMARKERS WITH DEUCRAVACITINIB TREATMENT IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS: RESULTS FROM THE PHASE 2 PAISLEY TRIAL

Christina Charles-Schoeman[1], Brittany Weber[2], Lu Gao[3], Eric F. Morand[4], Michelle Kahlenberg[5], Michael Garshick[6], Ilias Kouris[3], Chun Wu[3], Nathanial Eddy[3], Ian M. Catlett[3], Peter Schafer[3], Jinqi Liu[3]
[1]Division of Rheumatology, Department of Medicine, University of California Los Angeles, Los Angeles, United States of America, [2]Division of Preventive Cardiology, Division of Cardiovascular Imaging, Brigham and Women's Hospital, Boston, United States of America, [3]Bristol Myers Squibb, Princeton, United States of America, [4]School of Clinical Sciences, Monash University, Melbourne, Australia, [5]Department of Basic and Translational Research, Division of Rheumatology, University of Michigan, Ann Arbor, United States of America, [6]Ronald O. Perelman Department of Dermatology and Leon H. Charney Division of Cardiology, New York University Grossman School of Medicine, NYU Langone Health, New York, United States of America

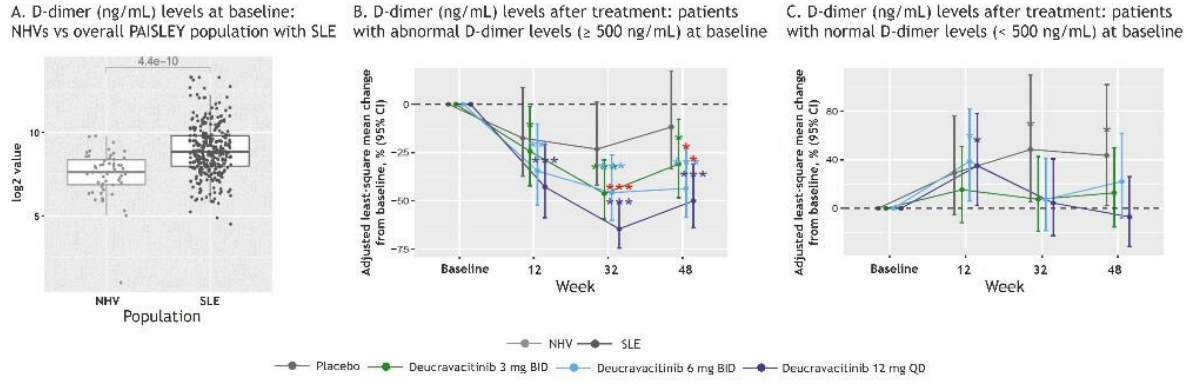
Background/Purpose: Patients with systemic lupus erythematosus (SLE) have a significantly higher risk of venous thromboembolism compared with the general population.[1] Elevated D-dimer levels have been used to predict risk for recurrent deep vein thrombosis and pulmonary embolism,[2] and D-dimer levels are associated with higher thrombosis risk irrespective of antiphospholipid antibodies in patients with SLE.[3] Deucravacitinib, an oral, selective, allosteric tyrosine kinase 2 (TYK2) inhibitor, has a unique mechanism of action and has shown efficacy in the phase 2 PAISLEY study in patients with SLE (NCT03252587). We used baseline D-dimer levels as a surrogate marker of thrombotic risk to investigate the impact of deucravacitinib or placebo on thrombosis-relevant biomarkers in patients with SLE with abnormal D-dimer levels from the PAISLEY study.

Methods: Samples from 319 patients with SLE were tested for D-dimer and Olink® Explore HT, covering > 5000 proteins. D-dimer levels were quantified by MLM Medical Labs with IMUCLONE D-dimer ELISA kits (BioMedica Diagnostics). Patients were categorized by baseline D-dimer value: normal (< 500 ng/mL, n = 174) or abnormal (≥ 500 ng/mL, n = 145). Fifty-four background-matched samples from normal healthy volunteers (NHVs) were also analyzed. Protein expression was compared in normal vs abnormal D-dimer groups. Changes in D-dimer levels were evaluated using linear

mixed-effects modeling; pre- and posttreatment thrombosis-relevant biomarkers were studied in patients with SLE with abnormal baseline D-dimer levels.

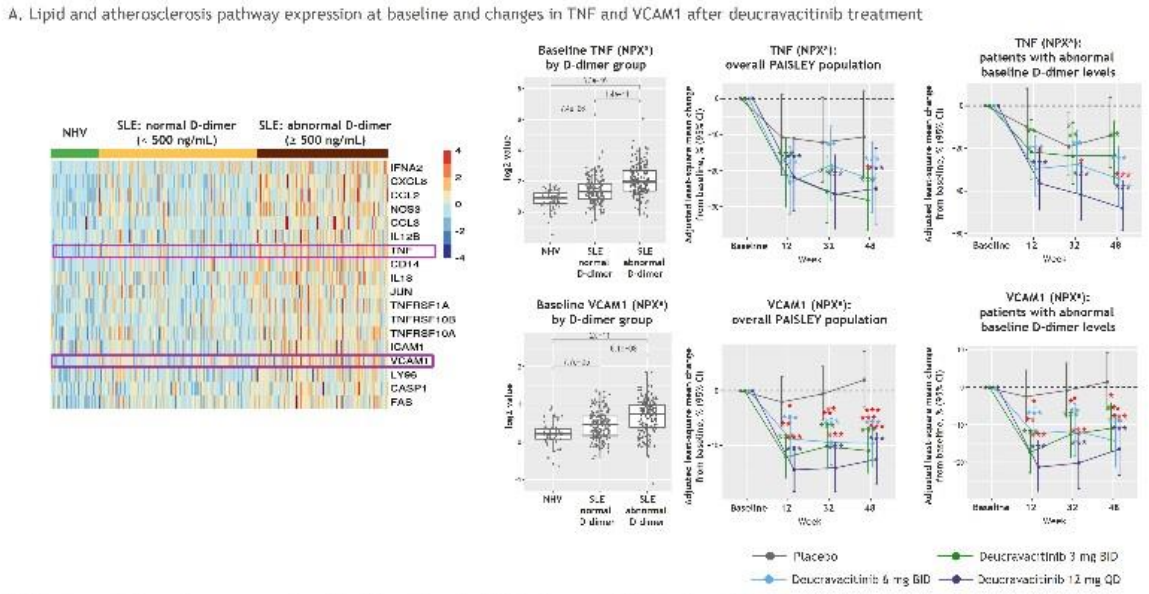
Results: Significantly higher D-dimer levels were observed in patients with SLE compared with NHVs ($P < 0.0001$; **Figure 1A**). All 3 doses of deucravacitinib significantly reduced D-dimer levels in patients with SLE with abnormal baseline D-dimer levels (**Figure 1B**). Meaningful reductions in D-dimer levels were not observed with deucravacitinib in patients with normal baseline D-dimer levels (**Figure 1C**). In patients with abnormal baseline D-dimer levels, 1590 serum proteins associated with 20 biological pathways were significantly upregulated compared with patients with normal baseline D-dimer levels (adj. $P < 0.05$; fold change > 1). The top 2 identified pathways enriched in upregulated proteins were cytokine/chemokine signaling and lipid/atherosclerosis pathways. Deucravacitinib led to the normalization of proteins mediating these pathways (eg, TNF, VCAM1, ICAM1; **Figure 2A**) in the overall population and patients with abnormal baseline D-dimer levels. Further investigation of specific thrombosis-relevant pathways suggested elevation of the corresponding biomarkers (eg, AXL, VWF, MERTK, PDGFRA, PLAUR, GAS6) in patients with SLE with abnormal baseline D-dimer levels, followed by an improvement induced by deucravacitinib in a dose-dependent manner (**Figure 2B**).

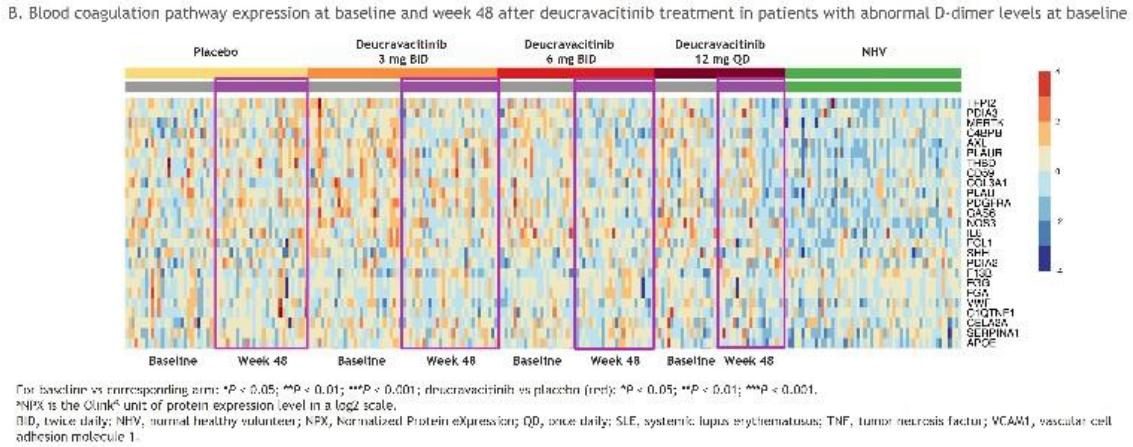
Figure 1. D-dimer levels at baseline and change from baseline after treatment with deucravacitinib or placebo in patients with SLE with normal or abnormal D-dimer levels at baseline



For baseline vs corresponding arm: *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; deucravacitinib vs placebo (red): *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.
BID, twice daily; NHV, normal healthy volunteer; QD, once daily; SLE, systemic lupus erythematosus.

Figure 2. Baseline biomarker expression relevant to lipid/atherosclerosis and coagulation pathways in patients with SLE with abnormal baseline D-dimer levels and change from baseline after deucravacitinib treatment at week 48





For baseline vs corresponding arm: *P < 0.05; **P < 0.01; ***P < 0.001; deucravacitinib vs placebo (rest): ^P < 0.05; ^^P < 0.01; ^^^P < 0.001.
*NPX is the Olink® unit of protein expression level in a log2 scale.
BID, twice daily; NHV, normal healthy volunteer; NPX, Normalized Protein eXpression; QD, once daily; SLE, systemic lupus erythematosus; TNF, tumor necrosis factor; VCAM1, vascular cell adhesion molecule 1.

Conclusions: Patients with SLE with elevated baseline D-dimer levels had increased serum levels of proteins involved in the mediation of inflammation, atherosclerosis, and thrombosis. Deucravacitinib reduced D-dimer levels and normalized biomarkers relevant to development of thrombosis. Further investigations will be conducted in large populations of patients with SLE from the ongoing phase 3 studies (NCT05617677, NCT05620407). **References** [1.] Menichelli D. Autoimmun Rev 2023;22:103447.
[2.] Eichinger S. JAMA 2003;290:1071-74.
[3.] Wu H. Clin J Am Soc Nephrol 2008;3:1628-36. **Acknowledgments** We thank the patients and families who made this study possible, as well as the clinical teams that participated. We also thank Zhaoqing Wang for data analysis. The study was supported by Bristol Myers Squibb. All authors contributed to and approved the abstract; professional medical writing and editorial assistance was provided by Stephanie V. Koebele, PhD, of Nucleus Global, funded by Bristol Myers Squibb.

O052 / #245

Topic: ***AS24 - SLE-Treatment***

ABSTRACT CONCURRENT SESSION 09: SLE THERAPY – REVISITING OLD DRUGS AND UNLOCKING HIDDEN POTENTIAL OF NEW MEDICATIONS
24-05-2025 10:40 AM - 11:40 AM

INTERVAL-CENSORED OUTCOMES AND FLARE RISK AFTER HYDROXYCHLOROQUINE TAPERING/CESSATION: SENSITIVITY ANALYSES OF SYSTEMIC LUPUS INTERNATIONAL COLLABORATING CLINICS (SLICC) INCEPTION COHORT DATA

Rima Kaddoura[1], Celline Almeida-Brasil[2], John Hanly[3], Murray Urowitz[4], Ann Clarke[5], Guillermo Ruiz-Irastorza[6], Caroline Gordon[7], Rosalind Ramsey-Goldman[8], Michelle Petri[9], Ellen Ginzler[10], Daniel J Wallace[11], Sang-Cheol Bae[12], Juanita Romero-Diaz[13], Mary-Anne Dooley[14], Christine Peschken[13], David Isenberg[15], Anisur Rahman[15], Susan Manzi[16], Soren Jacobsen[17], S. Sam Lim[18], Ronald Van Vollenhoven[19], Ola Nived[20], Andreas Jönsen[20], Diane L Kamen[21], Cynthia Aranow[22], Jorge Sanchez-Guerrero[4], Dafna D Gladman[4], Paul R Fortin[23], Graciela S. Alarcón[24], Joan . Merrill[25], Kenneth Kalunian[26], Manuel Ramos-Casals[27], Kristjan Steinsson[28], Asad Zoma[29], Anca Askanase[30], Munther A Khamashta[31], Ian Bruce[32], Murat Inanc[33], Luck Lukusa[2], Michal Abrahamowicz[1], Sasha Bernatsky[1,2]
[1]McGill University, Medicine, Montreal, Canada, [2]Research Institute of the McGill University Health Center, Montreal, Canada, [3]Dalhousie University, Halifax, Canada, [4]University of Toronto, Toronto, Canada, [5]University of Calgary, Calgary, Canada, [6]Biocruces Bizkaia Health Research Institute, Barakaldo, Spain, [7]University of Birmingham, Birmingham, United Kingdom, [8]Northwestern University, Chicago, United States of America, [9]John Hopkins University, Baltimore, United States of America, [10]SUNY Downstate Medical Center, New York, United States of America, [11]Cedars-Sinai Medical Center, Los Angeles, United States of America, [12]Hanyang University Hospital for Rheumatic Diseases,, Seoul, Korea, Republic of, [13]University of Manitoba, Winnipeg, Canada, [14]University of North Carolina at Chapel Hill, Chapel Hill, United States of America, [15]University College London, London, United Kingdom, [16]Allegheny Singer Research Institute, Allegheny Health Network, Pittsburgh, United States of America, [17]Copenhagen University Hospital Center for Rheumatology and Spine Diseases, Copenhagen, Denmark, [18]Emory University, Division Of Rheumatology, Atlanta, United States of America, [19]Amsterdam University Medical Centers, Department Of Rheumatology And Clinical Immunology, Amsterdam, Netherlands, [20]Lund University Faculty of Medicine, Lund, Sweden, [21]Medical University of South Carolina, Charleston, United States of America, [22]Feinstein Institute for Medical Research, Manhasset, United States of America, [23]Universite Laval, Quebec City, Canada, [24]Marnix E. Heersink School of

Medicine, Rheumatology, Birmingham, United States of America, [25]Oklahoma Medical Research Foundation, Clinical Immunology Program, Oklahoma City, United States of America, [26]University of California San Diego, San Diego, United States of America, [27]Universitat de Barcelona, Barcelona, Spain, [28]Landspitali University Hospital,, Reyjavik, Iceland, [29]Hairmyres Hospital, East Kilbride, United Kingdom, [30]Columbia University Medical Center, New York, United States of America, [31]St Thomas Hospital, London, United Kingdom, [32]Centre for Musculoskeletal Research, Division of Musculoskeletal and Dermatological Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, United Kingdom, [33]Istanbul University, Istanbul, Turkey

Background/Purpose: We previously evaluated hydroxychloroquine (HCQ) tapering/cessation and risk of systemic lupus erythematosus (SLE) flare in the SLICC Inception cohort. However, in our approach we did not account for potential bias due to interval censored (IC) outcomes, where exact timing of events are unknown. Our objective was to address this, with alternative approaches to defining timing of IC events, including the Simulation Extrapolation (SIMEX) approach.

Methods: We evaluated 1,543 members of the SLICC inception cohort (January 1999 to January 2019). Adults (18+) with SLE were enrolled in this cohort within 15 months of diagnosis and followed annually with questionnaires and physician assessment. In our time-to-event analyses, time-zero was defined as cohort entry if a subject was taking HCQ at the time, or the first prescription of HCQ otherwise. HCQ tapering/cessation was defined as the first cessation or decreased dose of HCQ and modeled as a binary time-varying exposure. Multivariable proportional hazard regression assessed associations between HCQ tapering/cessation and time to SLE flare, controlling for demographics (age, sex, race/ethnicity, region, education), baseline medication (steroids, immunosuppressives, biologics), enrollment year, time between diagnosis and cohort entry, smoking status, end-stage renal disease, and body mass index. Lupus flare was defined as the earliest of: A. Increase (from prior score) of at least 4 points in the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), B. Increase/initiation of SLE therapy (prednisone, immunosuppressive, or biologic), or C. SLE-related hospitalization. Since exact date of increased SLEDAI-2K was unknown, these represented IC events. We compared alternative analyses, imputing the IC event time at either the end- or the mid-point of the interval between the previous clinic visit and the visit when the outcome was reported. In sensitivity analyses we used SIMEX, a more sophisticated method based on simulations that allowed us to assess how the HR of interest changes with increasing time interval between adjacent visits. By extrapolating observed trends between the original and simulated data, we could correct the bias estimated to be within the original data, due to IC events.[1]

Results: Out of the total 1,543 subjects, 398 (25.8%) decreased or stopped their HCQ at some point during their follow-up and 1,187 experienced a disease flare (76.9%). When IC event times were imputed at the end of the relevant time interval, the adjusted HR for flare related to HCQ decrease/cessation was 1.43 (95% confidence interval, CI 1.24-1.66). When IC event times were imputed at the mid-point, the point estimate for the adjusted HR was slightly higher (1.53, 95% CI1.32-1.78). SIMEX correction yielded an even higher point estimate for the adjusted HR (1.68, bootstrapped 95% CI 1.44-2.02).

Conclusions: HCQ tapering/cessation was associated with greater flare risk regardless of how IC events were handled. Correcting imprecise timing of IC events tended to increase the strength of estimated associations, although confidence intervals overlapped. Limitations of these analyses include failure to account for disease status and/or other concomitant drug changes at tapering/cessation. Future analyses will address these issues (and stratify outcomes according to whether HCQ was tapered versus stopped). [1]Abrahamowicz M, Beauchamp ME, Moura CS, Bernatsky S, et.al Adapting SIMEX to correct for bias due to interval-censored outcomes in survival analysis with time-varying exposure. Biom J.. 2022;64(8):1467-1485. PMID:36065586

O053 / #469

Topic: ***AS24 - SLE-Treatment***

ABSTRACT CONCURRENT SESSION 09: SLE THERAPY – REVISITING OLD DRUGS AND UNLOCKING HIDDEN POTENTIAL OF NEW MEDICATIONS
24-05-2025 10:40 AM - 11:40 AM

COMPARATIVE SAFETY OF COMMON IMMUNOSUPPRESSANTS IN SLE: A CLINICAL TRIAL EMULATION ON INFECTION RISK WITH ADJUSTMENT FOR GLUCOCORTICOID DOSE

Ali Duarte-Garcia[1], Mariana González-Treviño[1], Cynthia Crowson[1,2], Rozalina Mccoy[3], Yihong Deng[1]
[1]Mayo Clinic, Rheumatology, Rochester, United States of America, [2]Mayo Clinic, Quantitative Health Sciences, Rochester, United States of America, [3]University of Maryland, Baltimore, United States of America

Background/Purpose: Serious infections are among the most common causes of death in SLE. We performed a clinical trial emulation to assess the comparative safety of four commonly used immunosuppressants for treating SLE.

Methods: Using the OptumLabs Data Warehouse, we identified adults ≥18 years with SLE, defined as ≥3 ICD9/10 codes separated by ≥30 but ≤365 days, who initiated treatment with methotrexate, azathioprine, belimumab, or mycophenolate mofetil (MMF) between March 1, 2011, and September 30, 2023. We required a ≥6-month washout period during which patients could not have been treated with any of the drugs being compared. We excluded those with a prior history of lupus nephritis or organ transplant. The primary outcome was hospitalizations for infections. We emulated randomization using inverse probability weighting and stabilized weights for the four study groups, balancing baseline covariates, including glucocorticoid use and dose, hydroxychloroquine use, and disease severity (per the Garris algorithm; details in Table 1). Patients were followed for up to 3 years, death, or disenrollment. We applied two censoring approaches: intention-to-treat (ITT) and per-protocol (PP). In the ITT analysis, patients were followed based on their initial medication; in the PP analysis, patients were censored if they stopped or switched drugs. We first conducted analyses using inverse probability weighting with only baseline covariates, then further adjusted for post-baseline prednisone doses using a Marginal Structural Model. We repeated the analysis using traumatic injuries as a falsification outcome.

Results: After weighting, 738 patients initiated belimumab, 2,462 methotrexate, 1,113 MMF, and 1,459 azathioprine. The mean age was 48 years, and more than 90% were women. Most patients were on background therapy with hydroxychloroquine (66.0% to 70.8%) and glucocorticoids (72.6% to 74.3%), and around 50% had moderate SLE

severity based on the Garris algorithm. Baseline covariates were balanced across groups after weighting (Table 1). Hospitalization rates for infections were highest with MMF, followed by azathioprine, methotrexate, and belimumab. In the baseline-only ITT analysis MMF showed significantly higher infection risk compared to belimumab (HR: 1.55, 95% CI 1.07-2.25, p = 0.02) and methotrexate (HR: 1.32, 95% CI 1.04-1.68, p = 0.02). The PP analysis confirmed higher infection risk with MMF compared to belimumab (HR: 2.27, 95% CI 1.11-4.62, p = 0.02). After adjusting for post-baseline prednisone doses, no significant differences were observed among the four drugs (Table 2). There were no differences in the cumulative incidence of traumatic injuries across all drugs, supporting internal
validity.

Table 1. Baseline Characteristics of SLE Patients on Immunosuppressants After Weighting
Demographics, comorbidities, SLE severity, and medication use for patients initiating azathioprine, belimumab, methotrexate, or MMF, with standardized mean differences (SMD) for group balance.

Characteristic	Azathioprine (n=1459)	Belimumab (n=738)	Methotrexate (n=2462)	Mycophenolate (n=1113)	SMD
Age, mean (SD)	48.58 (15.23)	48.07 (14.24)	48.86 (15.21)	48.44 (15.45)	0.028
Male, n (%)	120 (8.2)	52 (7.1)	217 (8.8)	105 (9.4)	0.046
Race/Ethnicity, n (%)					0.081
Asian	50 (3.5)	15 (2.0)	78 (3.2)	40 (3.6)	
Black	311 (21.3)	140 (18.9)	500 (20.3)	235 (21.1)	
Hispanic	205 (14.1)	108 (14.6)	361 (14.7)	173 (15.5)	
Unknown	67 (4.6)	40 (5.5)	102 (4.2)	54 (4.8)	
White	824 (56.5)	436 (59.0)	1420 (57.7)	612 (55.0)	
Comorbidities					
Elixhauser comorbidity index, mean (SD)	3.09 (2.10)	3.12 (2.16)	3.05 (2.12)	3.15 (2.17)	0.024
Diabetes, n (%)	166 (11.4)	85 (11.5)	304 (12.4)	118 (10.7)	0.028
Coronary artery disease, n (%)	111 (7.6)	54 (7.4)	192 (7.8)	91 (8.2)	0.016
Chronic kidney disease, n (%)	39 (2.7)	17 (2.3)	56 (2.3)	31 (2.8)	0.022
Cerebrovascular disease, n (%)	68 (4.7)	38 (5.1)	114 (4.6)	57 (5.1)	0.015
Smoking, n (%)	118 (8.1)	60 (8.1)	218 (8.8)	94 (8.4)	0.016
Medication Use					
Antimalarial, n (%)	973 (66.7)	522 (70.8)	1677 (68.1)	734 (66.0)	0.057
Glucocorticoid, n (%)	1084 (74.3)	540 (73.2)	1807 (73.4)	808 (72.6)	0.020
Other immunosuppressants, n (%)	79 (5.4)	50 (6.8)	133 (5.4)	52 (4.7)	0.045
Mean daily prednisone dose, mean (SD)	5.66 (13.32)	5.03 (11.39)	5.47 (12.09)	6.04 (13.35)	0.043
SLE Severity, n (%)					0.026
Mild	390 (26.7)	186 (25.2)	646 (26.3)	302 (27.2)	
Moderate	742 (50.9)	380 (51.5)	1247 (50.6)	559 (50.2)	
Severe	327 (22.4)	172 (23.3)	569 (23.1)	252 (22.6)	
Healthcare Utilization					
Emergency department visits, n (%)	473 (32.4)	232 (31.5)	772 (31.4)	370 (33.2)	0.023
Hospitalizations, n (%)	211 (14.5)	102 (13.8)	332 (13.5)	171 (15.3)	0.029
Pneumococcal vaccine, n (%)	52 (3.5)	34 (4.6)	111 (4.5)	48 (4.3)	0.027
Prior hospitalizations for infection, n (%)	71 (4.9)	22 (3.1)	100 (4.0)	62 (5.5)	0.069

Table 2. Risk of Infection-Related Hospitalizations by Immunosuppressant in Non-Renal SLE
Hazard ratios (HR) and 95% confidence intervals (CI) for infection-related hospitalizations, with intention-to-treat (ITT) and per-protocol (PP) analyses adjusted for baseline covariates and post-baseline prednisone doses. Significant p-values are bolded.

Comparison	Baseline Only Covariates		Adjusted for Post-Baseline Prednisone Doses	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Intention-to-Treat (ITT) Analysis				
Belimumab vs. Azathioprine	0.77 (0.53, 1.11)	0.16	0.84 (0.59, 1.20)	0.34
Methotrexate vs. Azathioprine	0.90 (0.72, 1.14)	0.38	0.89 (0.71, 1.12)	0.32
Mycophenolate vs. Azathioprine	1.19 (0.92, 1.54)	0.18	1.09 (0.84, 1.40)	0.52
Methotrexate vs. Belimumab	1.17 (0.83, 1.66)	0.37	1.06 (0.75, 1.50)	0.74
Mycophenolate vs. Belimumab	1.55 (1.07, 2.25)	**0.02**	1.30 (0.89, 1.88)	0.17
Mycophenolate vs. Methotrexate	1.32 (1.04, 1.68)	**0.02**	1.22 (0.95, 1.57)	0.12
Per-Protocol (PP) Analysis				
Belimumab vs. Azathioprine	0.49 (0.24, 0.99)	**0.046**	0.70 (0.37, 1.31)	0.26
Methotrexate vs. Azathioprine	0.76 (0.48, 1.20)	0.24	0.71 (0.47, 1.07)	0.10
Mycophenolate vs. Azathioprine	1.11 (0.69, 1.78)	0.67	1.08 (0.71, 1.65)	0.71
Methotrexate vs. Belimumab	1.56 (0.78, 3.09)	0.21	1.02 (0.55, 1.88)	0.95
Mycophenolate vs. Belimumab	2.27 (1.11, 4.62)	**0.02**	1.55 (0.81, 2.98)	0.19
Mycophenolate vs. Methotrexate	1.46 (0.91, 2.35)	0.12	1.52 (0.98, 2.37)	0.06

Conclusions: In this clinical trial emulation of comparative safety, adjusting for prednisone dose eliminated differences in infection-related hospitalization risk among the four studied immunosuppressants. These findings suggest that glucocorticoid dose, rather than the choice of immunosuppressant, may be the primary driver of serious infections in SLE.

O054 / #505

Topic: ***AS24 - SLE-Treatment***

ABSTRACT CONCURRENT SESSION 09: SLE THERAPY – REVISITING OLD DRUGS AND UNLOCKING HIDDEN POTENTIAL OF NEW MEDICATIONS
24-05-2025 10:40 AM - 11:40 AM

ADMINISTRATION OF BELIMUMAB IN EARLY ACTIVE LUPUS PATIENTS HINDERS ACCRUAL OF EULAR/ACR CRITERIA WITHIN THE FIRST 12 MONTHS OF TREATMENT

Mariele Gatto[1], Claudio Cruciani[1], Pietro Pilo[2], Elisa Bellis[2], Annamaria Iagnocco[2], Andrea Doria[3], Savino Sciascia[4]
[1]University of Turin, Academic Center For Rheumatology, Turin, Italy, [2]University of Turin, Academic Center For Rheumatology, Torino, Italy, [3]University of Padova, Rheumatology, padova, Italy, [4]University of Turin, San Giovanni Bosco Hub Hospital, Department Of Clinical And Biological Sciences, Turin, Italy

Background/Purpose: Addition of biologic drugs to standard of care (SoC) in systemic lupus erythematosus (SLE) is advised in refractory patients. Evidence is needed on the effectiveness of early biologic use in influencing SLE course. In this cohort study, we aim to assess the effect of belimumab administration on disease progression in early active lupus patients.

Methods: We performed a multicentric observational study on patients with early SLE receiving either belimumab or SoC alone and compared the rate of EULAR/ACR 2019 criteria (1) accrual between the two groups as a measure of lupus progression over time. Patients were defined as early active if they were diagnosed within 12 months from treatment initiation and displayed up to two EULAR/ACR clinical criteria, excluding major organ involvement, with active serology (i.e. positive anti-dsDNA antibodies and/or decreased serum complement). Clinical, demographic and serological data were collected in an anonymized fashion at baseline and at 3, 6, and 12 months. Kaplan-Meier curves with log-rank comparison were used to assess criteria accrual throughout the first 12 month of follow-up.

Results: We included 57 early active SLE patients, 24 (42.1%) receiving SoC alone and 33 (57.9%) receiving add on belimumab to SoC and followed up for at least 12 months from baseline. The groups were comparable in terms of age, gender, disease duration, background immunosuppression and overall disease activity at baseline. Patients doomed to early belimumab displayed higher mean SLICC and prednisone daily dosage **(Table 1)**. Overall, 8.7 events/100-patients years occurred in our cohort. Twenty-five percent of patients on SoC versus 3.2% of patients on early belimumab accrued at least one EULAR/ACR criterion throughout the follow-up (p=0.035). Patients on SoC displayed development of skin rash (2 cases), arthritis (1 case), lupus nephritis (1 case),

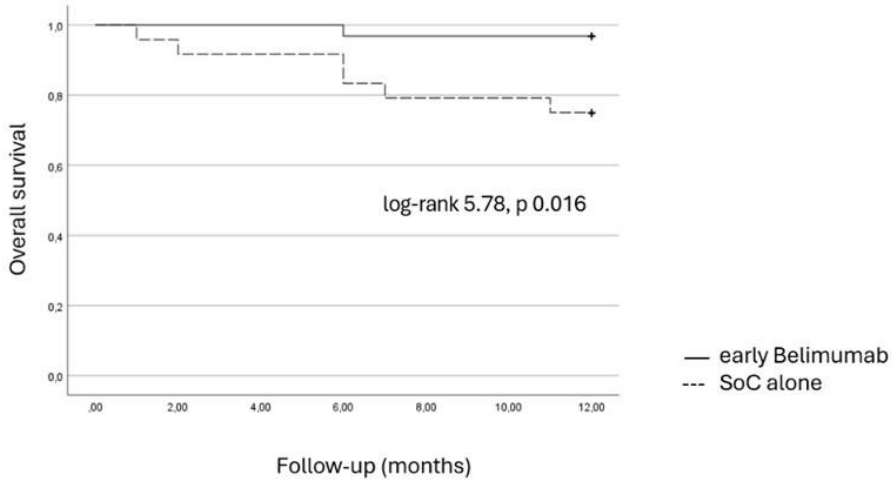
while one case of pericarditis occurred in the belimumab group. Criteria-free survival was significantly longer in patients receiving belimumab early as compared to those receiving SoC alone (**log-rank 5.78, p=0.016**) **Figure 1**. Mean time-to-event (months) was shorter in patients on SoC alone (10.3± 3.33 vs. 11.8±1.07, p=0.027).

Table 1. Baseline clinical and demographic features of early SLE patients

	Belimumab	**SoC**	**P**
Age	34.05±11.60	38.65±11.12	0.141
Gender, F (%)	29 (87.9)	23 (95.8)	0.385
HCQ n (%)	30 (90.9)	17 (70.8)	0.077
IS n (%)	26 (78.8)	21 (87.5)	0.494
Prednisone mg/d	8.75±6.67	5.00±10.61	0.054
Anti-dsDNA titers (kU/L)	201.04±282.95	88.91±46.86	0.020
C3 mg/dl	79.54±27.41	82.48±23.91	0.348
C4 mg/dl	12.00±5.12	10.77±3.53	0.180
cSLEDAI-2K	5.42±1.76	5.75±1.33	0.227
SLICC-DI	0.12±0.42	0.00±0.00	0.052

Continuous variables expressed as mean±SD. HCQ, hydroxycholoroquine; IS, immunosuppressants; cSLEDAI-2K, clinical SLE-activity index 2000; SLICC-DI, SLICC damage index **Figure 1. Kaplan-Meier curves depicting criteria-free survival in patient**

groups



Conclusions: Timely use of belimumab in patients with early active SLE can significantly delay disease progression, potentially preventing development of severe manifestations.

O055 / #488

Topic: *AS07 - Cutaneous Lupus*

ABSTRACT CONCURRENT SESSION 09: SLE THERAPY – REVISITING OLD DRUGS AND UNLOCKING HIDDEN POTENTIAL OF NEW MEDICATIONS
24-05-2025 10:40 AM - 11:40 AM

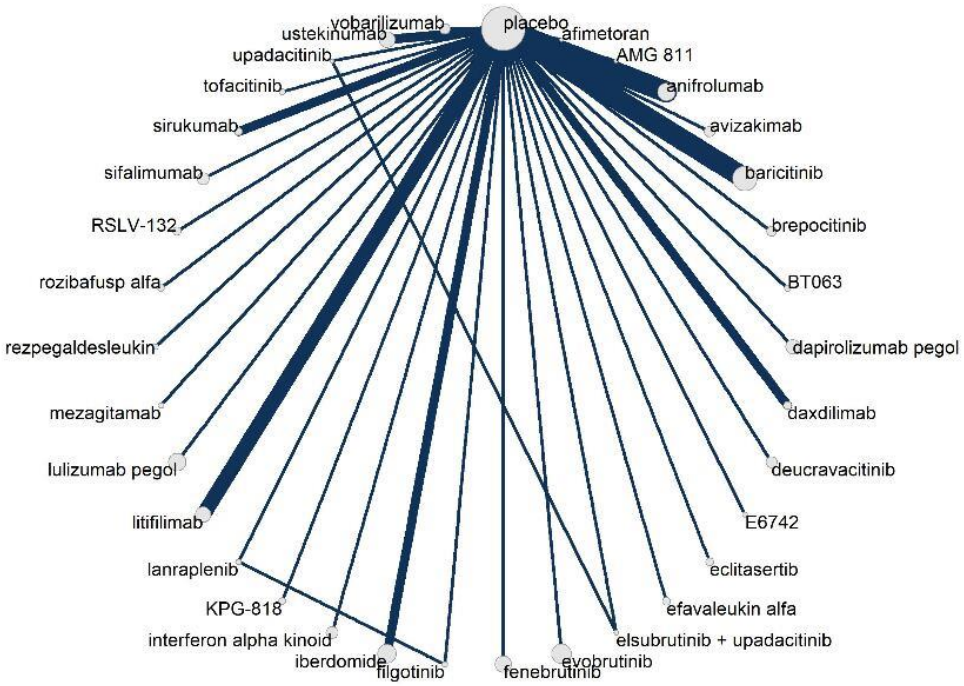
COMPARATIVE EFFECTS OF BIOLOGICS AND SMALL MOLECULE INHIBITORS ON CUTANEOUS DISEASE ACTIVITY IN SYSTEMIC AND CUTANEOUS LUPUS ERYTHEMATOSUS: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

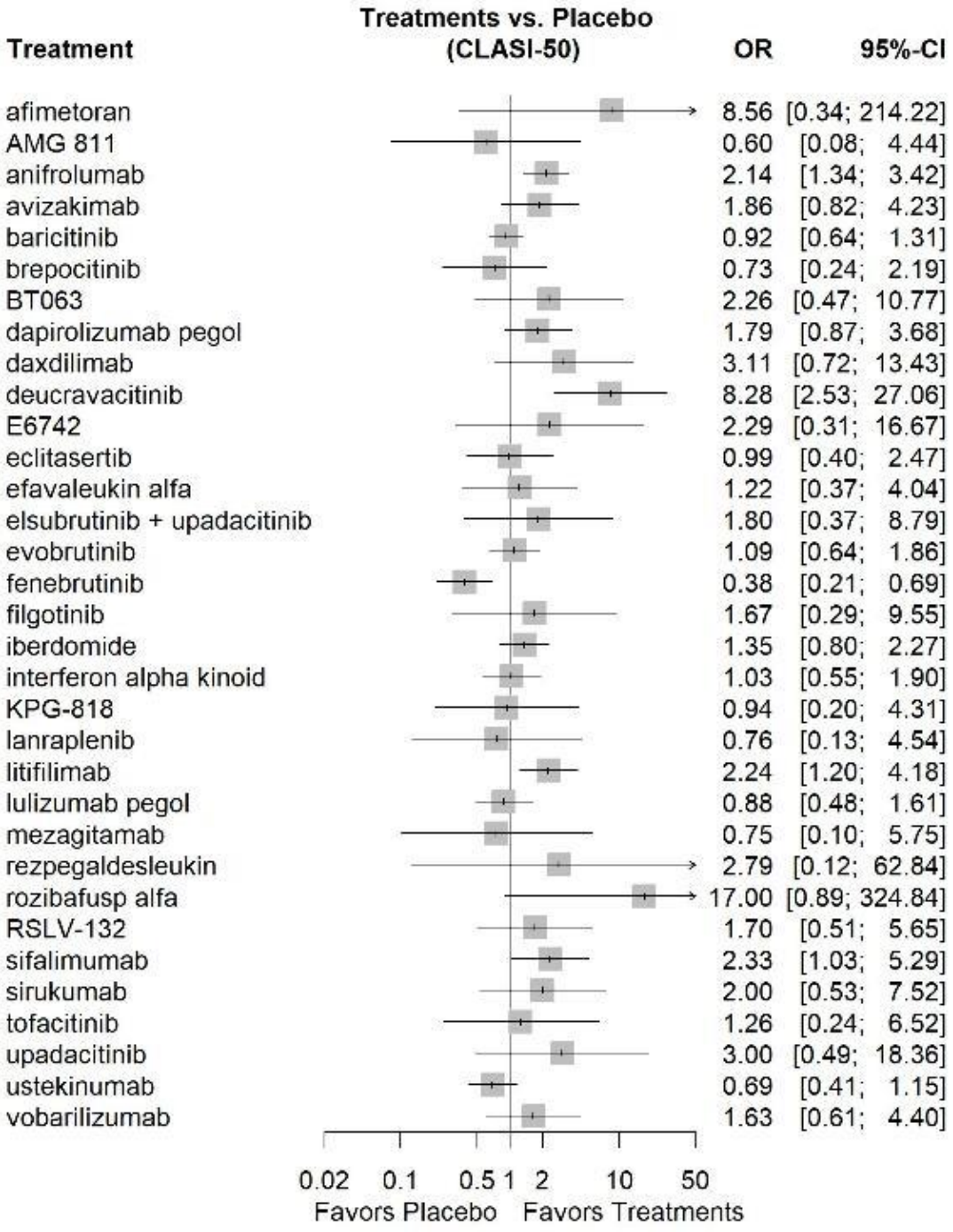
Daniel Rayner[1], David Gou[2], Cheng En Xi[3], Wayne Sun[1], Isabella Silang[2], Touraj Khosravi-Hafshejani[4], Jan Dutz[5]
[1]Western University, London, Canada, [2]McMaster University, Hamilton, Canada, [3]University of Ottawa, Ottawa, Canada, [4]University of Pennsylvania, Philadelphia, United States of America, [5]University of British Columbia, Vancouver, Canada

Background/Purpose: Cutaneous lupus erythematosus (CLE) is a debilitating and disfiguring disease that can occur with systemic lupus erythematosus (SLE) or independently. CLE is burdensome and impairs quality of life. Despite treatment with glucocorticoids, antimalarials, and traditional immunosuppressive treatments, cutaneous disease in LE represents an ongoing therapeutic challenge; yet biological agents and small molecule inhibitors show promise. The exclusion of most CLE patients from LE trials designed for SLE has resulted in a lack of approved treatments for CLE. Furthermore, skin disease improvement in LE is often only recorded as a secondary outcome in these trials. We conducted a systematic review and network meta-analysis to summarize the existing biological agents and small molecule inhibitors used to treat LE and their comparative effect on CLE disease activity.

Methods: We systematically searched MEDLINE, Embase, and CENTRAL to October 6th, 2024, for randomized controlled trials (RCTs) assessing the impact of biologics and/or small molecule inhibitors on cutaneous disease activity, as measured by Cutaneous LE Disease Area and Severity Index-Activity scores (CLASI-A, 0-70, lower scores better) in patients with cutaneous or systemic LE. Pairs of reviewers independently screened citations. We extracted relevant trial characteristics and CLASI-A outcome data according to the intention-to-treat principle and assessed risk of bias using Cochrane's Risk of Bias 2.0 tool for RCTs. Random effects network meta-analyses pooled effect estimates for the probability of achieving CLASI-50 (a 50% improvement in baseline CLASI-A scores). We applied the GRADE approach to inform our ratings of the certainty of evidence.

Results: We identified 43 unique RCTs randomizing 8,725 patients with systemic or cutaneous LE (median [range] of mean age: 42.8 [30.6-54.0] years; median 93% female). Most RCTs evaluated improvement in CLASI-A scores as a secondary outcome (n = 39, 91%). The median (range) CLASI-A score at baseline was 7.8 (2.53-23.5) points. A total of 33 unique interventions were evaluated across the included studies (Figure 1). Seven (16%) trials were judged to be at a high risk of bias, with common reasons being early termination of the trial and high rates of missing outcome data. Compared to placebo, high certainty evidence shows that anifrolumab increases the probability of achieving CLASI-50 (odds ratio [OR] 2.14, 95% CI 1.34-3.42; risk difference [RD] 18.8% more, 95% CI 7.3%-29.1%; Figure 2). Moderate certainty evidence suggests that deucravacitinib (OR 8.28, 95% CI 2.53-27.06; RD 43.2% more, 95% CI 22.6%-52.3%), litifilimab (OR 2.24, 95% CI 1.20-4.18; RD 19.8% more, 95% CI 4.5%-32.9%), and sifalimumab (OR 2.33, 95% CI 1.03-5.29; RD 20.7% more, 95% CI 0.7%-37.0%) increase the probability of achieving CLASI-50. Low certainty evidence suggests that daxdilimab (OR 3.11, 95% CI 0.72-13.43; RD 27.1% more, 95% CI 7.8% fewer to 48.0% more) may increase the probability of achieving CLASI-50. Baricitinib and iberdomide probably have little to no difference on CLASI-50 responses (moderate certainty) and brepocitinib may have little to no difference on CLASI-50 responses (low certainty).





Conclusions: Among patients with systemic or cutaneous LE, anifrolumab, deucravacitinib, litifilimab, and sifalimumab increased the probability of achieving CLASI-50 response compared to placebo. These agents act by inhibiting part of the type-1 interferon pathway and may have clinical utility in improving the lives of CLE patients.

O056 / #121

Topic: ***AS23 - SLE-Diagnosis, Manifestations, & Outcomes***

ABSTRACT CONCURRENT SESSION 09: SLE THERAPY – REVISITING OLD DRUGS AND UNLOCKING HIDDEN POTENTIAL OF NEW MEDICATIONS
24-05-2025 10:40 AM - 11:40 AM

STUDY OF ANTI-MALARIALS IN INCOMPLETE LUPUS – THE SMILE TRIAL

Nancy Olsen[1], Duanping Liao[2], Judith James[3], Joel Guthridge[3], Cristina Arriens[3], Diane L Kamen[4], Mariko Ishimori[5], Daniel J Wallace[5], Christopher Striebich[6], Benjamin Chong[7], Eric Schaefer[2], Vernon Chinchilli[2], David Karp[7]
[1]Penn State MS Hershey Medical Center, Medicine, Hershey, United States of America, [2]Penn State College of Medicine, Public Health Sciences, Hershey, United States of America, [3]Oklahoma Medical Research Foundation, Oklahoma City, United States of America, [4]Medical University of South Carolina, Charleston, United States of America, [5]Cedars-Sinai Medical Center, Los Angeles, United States of America, [6]University of Colorado School of Medicine, Anschutz, Medicine, Aurora, United States of America, [7]University of Texas Southwestern Medical Center, Dallas, United States of America

Background/Purpose: Patients with features of systemic lupus erythematosus (SLE) who do not have sufficient criteria to be classified can be designated as having incomplete lupus (ILE). This is a common condition seen in clinical practice and it has further significance as a group that has high risk of progression to SLE. Identification and treatment of those at risk has the potential to reduce the severity and incidence of SLE.

Methods: Based on previous studies, hydroxychloroquine (HCQ) was chosen as an intervention for a randomized, double-blind, placebo-controlled trial to determine whether the rate of accumulation of clinical and immunologic features of SLE as defined by the 2012 SLICC criteria could be reduced. ILE was defined as ANA positivity with one or two additional criteria from the SLICC 2012 list. Males and females 15 to 49 years of age were eligible for enrollment. After baseline evaluation including ophthalmologic exam, participants were randomized 1:1 to HCQ or placebo. Evaluations at 3-month intervals included clinical and laboratory measures as well as patient-reported outcomes (PROs). Treatment was continued for 24 months, but if SLICC criteria were satisfied sooner, patients exited the study. Ophthalmologic exams were carried out at conclusion of treatment.

Results: A total of 187 ILE patients were randomized at 7 sites in the USA. After excluding 7 patients found to have SLE criteria at baseline when pending laboratory data were completed, 180 patients were available for analysis; 92 were randomized to HCQ

and 88 received placebo. The mean age was 33 years, 91.1% were female and 74.4% were white individuals. At randomization, 65.6% had 2 SLICC criteria; the remainder had 3 SLICC criteria. The most common manifestations involved skin and joints. SLE per criteria developed in 24 participants (13.3%) during the trial who were terminated early and 40 (22%) developed additional SLICC criteria. The primary outcome was the rate of acquisition of SLICC criteria analyzed via a generalized linear mixed effects model, with an embedded ordinal logistic regression, comparing the changes over time for the two arms. This showed similar slopes in the two groups (P=0.72). The odds of progressing to a higher SLICC score relative to the previous score was 14% smaller for every 3-month increase in time for the HCQ group and 18% smaller for the placebo group, a difference which was not statistically significant (P=0.69). A key secondary outcome was time to progression to SLE. Using a Cox proportional hazards regression model, the hazard of progressing to SLE was 10% higher for the HCQ group than for placebo, which was not a statistically significant difference (P=0.81). Adverse events were similar in the two groups and no serious adverse events related to use of HCQ were recorded. Five individuals were excluded from entry due to abnormal ophthalmologic findings; none developed during the trial.

Conclusions: The SMILE results do not endorse the use of HCQ to prevent accumulation of SLICC SLE criteria. However, the definition of ILE used in SMILE does include individuals who are at risk for progressive disease and may be useful in future studies of preventive therapies. Other ongoing analyses will determine whether autoantibodies, inflammatory mediators or PROs were related to progressive illness or use of HCQ.

O056a / #846

Topic: *AS15 - Lupus Nephritis-Clinical*
Late-Breaking Abstract

ABSTRACT CONCURRENT SESSION 09: SLE THERAPY – REVISITING OLD DRUGS AND UNLOCKING HIDDEN POTENTIAL OF NEW MEDICATIONS
24-05-2025 10:40 AM - 11:40 AM

COMPLETE RENAL RESPONSES AND SAFETY FOR BELIMUMAB VERSUS PLACEBO IN A POST HOC MYCOPHENOLATE MOFETIL SUBGROUP WITH ACTIVE PROLIFERATIVE LUPUS NEPHRITIS

Richard Furie[1], Hans-Joachim Anders[2], George Bertsias[3], Ana Delgado[4], Roger Levy[5], Paula Curtis[6], Ciara O'Shea[7], Ryan Tomlinson[8], Brad Rovin[9]
[1]Zucker School of Medicine at Hofstra/Northwell, Great Neck, United States of America, [2]Department of Medicine IV, Hospital of LMU Munich, Munich, Germany, [3]University of Crete Medical School, Rheumatology And Clinical Immunology, Heraklion, Greece, [4]Immunology Medical Affairs, GSK, London, United Kingdom, [5]GSK, Global Medical Affairs, Collegeville, United States of America, [6]Statistics, GSK, London, United Kingdom, [7]GSK, Rheumatology Global Medical Affairs, Dublin, Ireland, [8]Development – R&D, GSK, Collegeville, United States of America, [9]Ohio State University Wexner Medical Center, Internal Medicine/nephrology, Columbus, United States of America

Background/Purpose: Belimumab, a human IgG1λ monoclonal antibody that selectively binds B lymphocyte stimulator, was first approved in 2011. It is the only biologic approved for both lupus nephritis (LN) and systemic lupus erythematosus (SLE). With greater than 10 years of real-world experience, EULAR acknowledged early use of belimumab in SLE, and ACR recommends its use in LN.
Reinforcing the central role of B-cells in LN immunopathogenesis, phase 3 trials successfully investigated belimumab (BLISS-LN; NCT01639339 [1]) and obinutuzumab (REGENCY; NCT04221477) in biopsy-proven active LN plus standard therapy (ST). Study differences (e.g. populations, concomitant medications, endpoint timings and definitions) present challenges in comparing LN trial outcomes. In this regard, BLISS-LN's unique design allowed inclusion of pure ISN/RPS class V and cyclophosphamide ST. To better align with the design of the REGENCY and NOBILITY (NCT02550652) trials, we analyzed *post hoc* a BLISS-LN subgroup of patients with active class III or IV LN ± concomitant class V who received mycophenolate mofetil (MMF) ST (i.e. excluding pure class V and cyclophosphamide ST).

Methods: BLISS-LN was a 104-week global trial of 448 adult patients with active class III or IV (± concomitant class V) or pure class V LN [1]. Key features of the BLISS-LN study design (**Table 1**) included a stringent complete renal response (CRR) definition

that differs from other trials (BLISS-LN-CRR defined as urinary protein-to-creatinine ratio [uPCR] <0.5, eGFR ≤10% below the pre-flare value or ≥90 mL/minute/1.73 m^2, and no rescue therapy) [1]. Additionally, BLISS-LN-CRR defined treatment failure as use of prohibited therapy and not achieving mandatory prednisone taper to ≤10 mg/day by Week 24.

Results: Of the overall 448 patients in BLISS-LN, 271 had active class III or IV LN ± concomitant class V and received MMF ST. CRR data for this subgroup (referred to as the "MMF subgroup") using pre-specified definitions are shown in **Table 2**. At Week 76 in the MMF subgroup, BLISS-LN-CRR treatment difference between belimumab and placebo was 11.3% for class III or IV ± concomitant class V, and 12.2% for class III or IV only. At Week 104, BLISS-LN-CRR treatment difference was 14.9% for class III or IV ± concomitant class V, and 17.4% for class III or IV only.
Regarding safety, in the BLISS-LN MMF subgroup, serious adverse events up to Week 104 were lower with belimumab (24.4%, n=40/164) than placebo (32.1%, n=53/165).

Conclusions: Building on the extensively demonstrated safety [2] and efficacy profiles of belimumab across SLE and LN, this *post hoc* subgroup analysis of patients with active class III or IV LN ± concomitant class V receiving MMF in BLISS-LN demonstrated enhanced renal responses with belimumab versus placebo at Weeks 76 and 104. This improved outcome is also observed when compared to the overall BLISS-LN population [1]. Belimumab has additionally been shown to be safe and efficacious in patients with LN in the real world [3]. Benefit/risk profiles, real-world effectiveness and data from extra-renal SLE should be considered to inform LN treatment decisions.

Table 1: Key Features of the BLISS-LN Study Design

Study Design Component	BLISS-LN (Belimumab – NCT01639339)
Key Endpoints	Primary endpoint: PERR at Week 104 Key secondary endpoint: CRR at Week 104
PERR Definition	uPCR ≤0.7; eGFR no worse than 20% below the pre-flare value or ≥60 ml/min/1.73 m², and prednisone dose ≤10 mg/day at Week 24; and no rescue therapy except for short-term rescue in Weeks 24–76 for reasons other than LN. No GC rescue treatments were allowed in Weeks 76–104
CRR Definition	uPCR <0.5; eGFR no worse than 10% below the pre-flare value or ≥90 ml/min/1.73 m², and prednisone dose ≤10 mg/day at Week 24; and no rescue therapy except for short-term rescue in Weeks 24–76 for reasons other than LN. No GC rescue treatments were allowed in Weeks 76–104
Recruitment	N = 448; Americas, Europe, China, South Korea, Thailand, Taiwan, Philippines
LN Classes	Class III or IV (± concomitant class V), or pure class V LN
Study Treatment Procedure	Belimumab IV 10 mg/kg every 28 days to Week 100
Standard Therapy (Excluding GC)	Induction therapy with IV CYC (500 mg every 2 weeks) or MMF (target 3 g/day). Maintenance therapy of AZA (2 mg/kg per day) or MMF (1–2 g/day)
GC Use at Induction	Oral prednisone (≤60 mg/day) Optional 1–3 IV methylprednisolone pulses (500–1000 mg each) at induction
GC Tapering Schedule	Mandatory taper to ≤10 mg/day prednisone by Week 24, as part of PERR and CRR endpoints. Permitted short-term rescue treatment between Weeks 24 and 76 for non-LN reasons. Patients violating GC regimen rules considered as treatment failures
Prohibited Medications	B-cell therapy and any non-belimumab biologics. CYC induction within 3 months before trial initiation
Premedication	None required

AZA, azathioprine; CRR, complete renal response; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; IV, intravenous; PERR, primary efficacy renal response; uPCR, urinary protein-to-creatinine ratio.

Table 2: BLISS-LN CRR Responder Data at Weeks 76 and 104 for a Subgroup of Patients Receiving MMF with Active Class III or IV LN ± Concomitant Class V

	CRR Class III or IV Pure Proliferative (MMF Subgroup)*		CRR Class III or IV + V Mixed Proliferative/ Membranous (MMF Subgroup)*		CRR† Class III or IV ± Concomitant Class V Pure Proliferative and Mixed Proliferative/ Membranous (MMF Subgroup)*	
	BEL (n=94)	**PBO (n= 96)**	**BEL (n=41)**	**PBO (n=40)**	**BEL (n=135)**	**PBO (n=136)**
Week 76						
CRR Responders	37.2%	25.0%	29.3%	20.0%	34.8%	23.5%
Treatment Difference vs PBO	12.2%		9.3%		11.3%	
Week 104						
CRR Responders	35.1%	17.7%	26.8%	17.5%	32.6%	17.6%
Treatment Difference vs PBO	17.4% OR: 2.34‡ (95% CI: 1.17–4.69)		9.3% OR: 1.86‡ (95% CI: 0.61–5.66)		14.9%	

*Data shown are for a *post hoc* subgroup of patients who received MMF standard therapy (No CYC). †CRR responder rates for the combined subgroups "Class III or IV" and "Class III or IV + V" were manually calculated using data on the number of responders in each subgroup. ‡OR adjusted for race, baseline uPCR and baseline eGFR.

BEL, belimumab; CRR, complete renal response; CI, confidence interval; MMF, mycophenolate mofetil; OR, odds ratio; PBO, placebo.

References

[1.] Furie R. N Engl J Med 2020;383:1117-28.

[2.] Wallace D. Arthritis Rheumatol 2019;71:1125-34.

[3.] Gatto M. J Autoimmun 2021;124:1027-29. **Funding:** GSK

O057 / #226

Topic: ***AS15 - Lupus Nephritis-Clinical***

ABSTRACT CONCURRENT SESSION 10: INTEGRATING PROTEOMIC & TRANSCRIPTOMICS IN SLE
24-05-2025 10:40 AM - 11:40 AM

NONINVASIVE URINARY PROTEOMICS PROVIDES VALUABLE INSIGHT INTO THE MOLECULAR CHARACTERISTICS FOR LUPUS NEPHRITIS

Meng Tan[1], Dongdong Zhan[2], Fang Cheng[2], Xiaojing Sun[1], Yi Wang[3], Jun Qin[3], Ying Tan[1]
[1]Peking University First Hospital, Beijing, China, [2]Department of Bioinformatics, Beijing Pineal Diagnostics Co, Beijing, China, [3]State Key Laboratory of Proteomics, Beijing Proteome Research Center, National Center for Protein Sciences (Beijing),Beijing Institute of Lifeomics, beijing, China

Background/Purpose: Lupus nephritis (LN) is a common complication of systemic lupus erythematosus that presents a high risk of end-stage renal disease. Clinically, the therapy of lupus nephritis mainly depends on the renal pathological LN classification by renal biopsy. However, the renal biopsy could not repeated as much as clinically request for invasiveness and the renal outcomes are still unsatisfactory. Thus, non-invasive tools stratifying LN patients are urgently needed.

Methods: Here, we collected 112 urine samples from LN patients on the day before they received renal biopsy and performed in-depth urine proteomics test. Associations between urinary proteomic analysis with clinical features, pathological data, and laboratory findings were further investigated.

Results: Unsupervised clustering distinguished four molecular subtypes (type1-4). Type 1 was marked with high expression of immunomodulatory proteins and associated with renal pathological findings of higher LN pathological acute index (AI) including more cellular/cytofibrous crescent and increased leukocyte infiltration in glomeruli. Clinically, patients with type 1 showed a higher proportion of renal response rate (83%) to prednisone combined with mycophenolate mofetil. In patients with type 2, keratins were significantly upregulated, indicating their role in cell structure maintaining. Type 3 displayed the overactivation of complement system with higher expression of complement from three to nine and regulatory protein of factor B and D, which might suggest potential therapeutic of complement inhibitors like eculizumab or iptocapan. Clinically, patients with type 3 showed more acute and chronic renal function injury. Type 4 was characterized by metabolic abnormalities and overexpression of SLC5A1 emerged as a distinctive hallmark. The patients with type 4 had higher rate of proteinuria and lower treatment response rate to standard therapy (55%) with stable renal function.

Conclusions: Noninvasive urinary proteomics provides valuable insight into the molecular characteristics and suggest new biomarkers of precise treatment in lupus nephritis

O058 / #380

Topic: ***AS12 - Genetics, Epigenetics, Transcriptomics***

ABSTRACT CONCURRENT SESSION 10: INTEGRATING PROTEOMIC & TRANSCRIPTOMICS IN SLE
24-05-2025 10:40 AM - 11:40 AM

LINKING TRANSCRIPTOMIC PROFILES OF KIDNEY AND BLOOD SAMPLES PROVIDES INSIGHT INTO IDENTIFICATION OF LUPUS NEPHRITIS

Andrea Daamen[1], Kathryn Kingsmore[1], Prathyusha Bachali[1], Nan Shen[2], Amrie Grammer[1], Peter Lipsky[1]
[1]AMPEL BioSolutions, Charlottesville, United States of America, [2]Shanghai Institute of Rheumatology, Shanghai, China

Background/Purpose: Current clinical methods to diagnose and evaluate the severity of lupus nephritis (LN) rely on identification of kidney dysfunction followed by invasive kidney biopsies. Here, we sought to identify molecular profiles of LN in the kidney tissue that would be reflected in blood gene expression.

Methods: Gene expression was analyzed from 46 kidney biopsies for which renal disease classification had been carried out by a blinded clinical pathologist and 91 blood samples from lupus patients with or without biopsy documented LN. For blood samples from patients with LN, biopsies were taken at the time of blood draw. Each dataset was analyzed by Gene Set Variation Analysis (GSVA) for enrichment of gene modules identifying immune cells/pathways, metabolism pathways, and kidney tissue cells. Samples were clustered using k means and ordered based on ISN/RPI classification of disease involvement.

Results: GSVA and unsupervised k-means clustering of kidney tissue identified four subsets of LN (**Fig. 1a**). Subsets 1-3 exhibited molecular profiles indicative of increasing severity, including upregulation of immune/inflammatory modules, decrease in metabolism modules and decrease in kidney tissue modules. Subset 4 was characterized by de-enrichment of immune modules and restored enrichment of metabolism and kidney tissue modules, but retained a loss of the podocyte and proximal tubule gene modules indicative of a post-inflammatory state and end organ damage. The molecular profile of each subset was associated with the ISN/RPI histologic classification (**Fig. 1b-d**). Subset 1 was dominated by Class II mesangial LN and Class V membranous LN with low activity and chronicity indices. Subset 2 contained the majority of Class III, focal, proliferative LN patients and increased activity and chronicity indices compared to Subset 1. The most active disease cluster, Subset 3, largely consisted of Class IV, diffuse proliferative LN patients with the highest overall activity and chronicity scores. Finally, Subset 4 was dominated by Class V LN patients.

Gene modules used to separate LN kidney biopsies were able to stratify blood gene expression from lupus patients with or without LN (**Fig. 2a**). Blood samples from LN patients were largely in Subsets 3-4 and mean SLEDAI was significantly increased in Subset 3 (**Fig. 2b**). Among the LN patients, Subset 3 had the highest activity index and Subsets 1 and 4 had the highest chronicity indices (**Fig. 2c-d**).

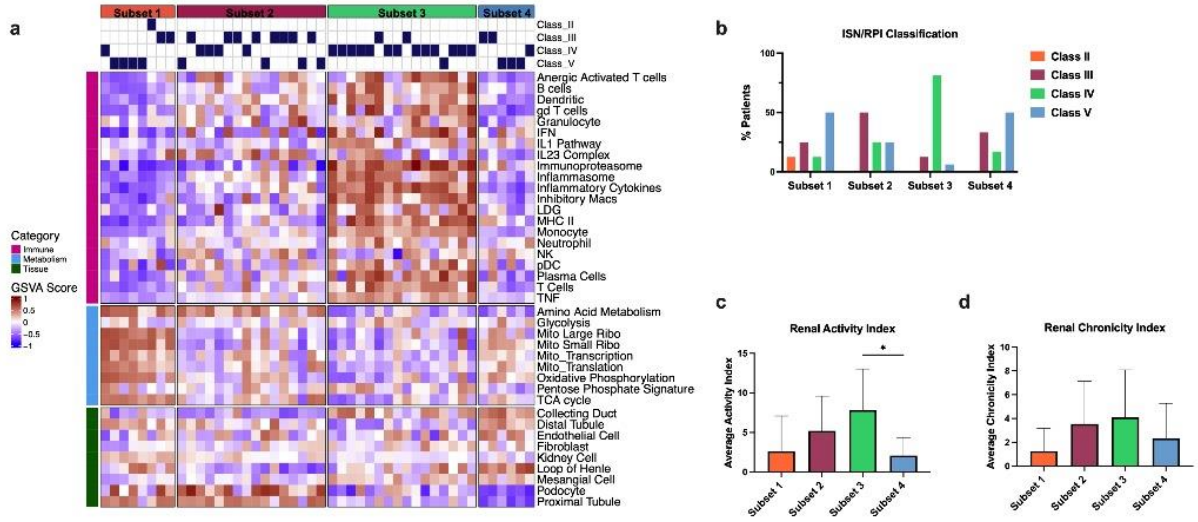


Figure 1: Gene expression based clustering and clinical evaluation of LN kidney biopsies. (a) GSVA heatmap of 46 LN patients with histological classification for enrichment of immune, metabolism, and kidney tissue gene modules. (b) ISN histological kidney classification for patients in each subset. Average renal activity (c) and chronicity (d) indices for kidney biopsies from each subset.
*p<0.05

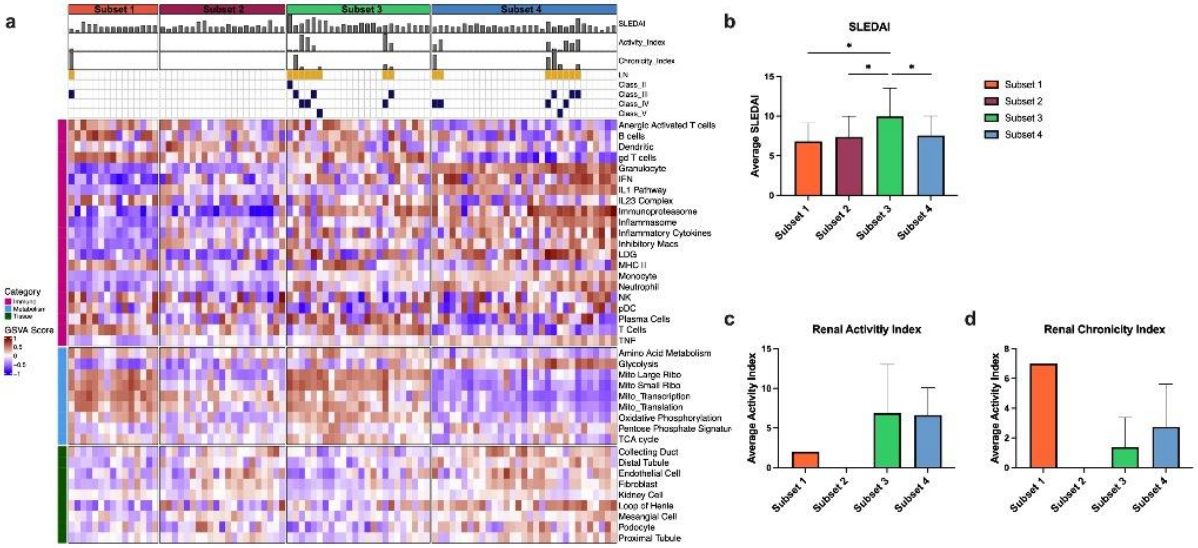


Figure 2: Gene expression based clustering and clinical evaluation of blood from lupus patients. (a) GSVA heatmap of 91 lupus patients with or without LN for enrichment of immune, metabolism, and kidney tissue gene modules. (b) Average SLEDAI for patients in each subset. Average renal activity (c) and chronicity (d) indices for LN patients with kidney biopsies in each subset. *p<0.05

Conclusions: Gene expression analysis of LN kidney biopsies revealed four subsets with distinct profiles of gene module enrichment indicative of immune involvement, metabolic dysfunction, and tissue damage that aligned with histologic class. Although there was greater heterogeneity between subsets in the blood as compared to the kidney, distinct gene profiles associated with higher disease severity and LN activity were identified.

O059 / #244

Topic: ***AS16 - Lupus Nephritis-Pathogenesis***

ABSTRACT CONCURRENT SESSION 10: INTEGRATING PROTEOMIC & TRANSCRIPTOMICS IN SLE
24-05-2025 10:40 AM - 11:40 AM

THE IMMUNE MAP OF LUPUS NEPHRITIS: A SPATIALLY-RESOLVED KIDNEY PROTEOMIC APPROACH.

Chen-Yu Lee[1], M. Caleb Marlin[2], Xiaoping Yang[3], Vasileios Morkotinis[2], Alessandra Celia[1], Jill P. Buyon[4], Richard Furie[5], Diane L Kamen[6], Jeff Hodgin[7], Chaim Putterman[8], Jennifer Barnas[9], Kenneth Kalunian[10], Peter Izmirly[4], Betty Diamond[5], Anne Davidson[5], The Accelerating Medicines Partnership In Ra/Sle[11], Judith James[2], Michelle Petri[1], Joel Guthridge[2], Avi Rosenberg[3], Andrea Fava[1]
[1]Johns Hopkins University, Rheumatology, Baltimore, United States of America, [2]Oklahoma Medical Research Foundation, Arthritis & Clinical Immunology, Oklahoma City, United States of America, [3]Johns Hopkins University, Division Of Kidney-urologic Pathology, Baltimore, United States of America, [4]New York University School of Medicine, Medicine, New York, United States of America, [5]Institute of Molecular Medicine, Feinstein Institutes for Medical Research, Manhasset, United States of America, [6]Medical University of South Carolina, Division Of Rheumatology, Charleston, United States of America, [7]University of Michigan, Department Of Pathology, Ann Arbor, United States of America, [8]Albert Einstein College of Medicine, Department Of Medicine, Bronx, United States of America, [9]University of Rochester Medical Center,, Division Of Rheumatology, Rochester, United States of America, [10]University of California, San Diego School of Medicine, Division Of Rheumatology, Autoimmunity And Inflammation, San Diego, United States of America, [11]Multiple Institutions, Multiple Cities, United States of America

Background/Purpose: Treatment response in lupus nephritis (LN) remain inadequately low, highlighting the need for better understanding of LN pathogenesis to improve management. Single-cell transcriptomic studies are providing an unprecedented catalog of cell states in LN, yet their spatial organization is not well understood. Since structure underlies function, we aim to map the spatial organization of immune cells in LN.

Methods: We developed a serial immunohistochemistry (sIHC) workflow (18-plex), followed by imaging and destaining cycles. Image processing was performed using HALO (Indica Labs), including AI-assisted tissue classification. PCA was used for dimensional reduction, and KNN and SNN algorithms were applied to identify immune cell types based on their markers' fluorescent intensity. Immune cell aggregates in the tissues were defined using DBSCAN as a minimum of 3 cells within a radius (epsilon) of

50 µm to infer interactions between cells. Aggregate sizes were categorized into small (3-29 cells), medium (30-99 cells), and large (>100 cells) based on the frequency distribution (**Fig. 1A-B**). The proportion of immune cell types in each aggregate was used for K-means clustering to determine aggregate subtypes. Clinical features were correlated with each aggregate subtype using Pearson's correlation coefficient (**Fig. 2**).

Results: In this analysis, we included 29 kidney biopsies of LN resulting in 1,913,845 cells (182,783 immune cells). We identified 12,371 cellular aggregates. Most (97%) aggregates were small (<30 cells) (**Fig. 1C-D**); however, medium and large aggregates included 33.7% of immune cells. Glomerular aggregates were numerically increased in proliferative and mixed classes (**Fig. 1E**). These were small and primarily composed of CD68+ myeloid cells (**Fig. 2A**). Glomerular aggregates rich in CD68+ cells negatively correlated with UPCR, while aggregates rich in lymphocytes negatively correlated with chronicity (**Fig. 2A**). In contrast, tubulointerstitial (TI) aggregate density was similar across LN classes (**Fig. 1E**) and negatively correlated with GFR. Significant heterogeneity in aggregate composition revealed >10 aggregate subtypes according to composition and size (**Fig. 2**). Small aggregates tended to be restricted to 1-2 cell types each, while medium and large aggregates included mixed proportions of CD4+ T, CD8+ T, B, dendritic, myeloid, and plasma cells, suggesting germinal center-like structures (**Fig. 2**). Distinct TI aggregate subtypes associated with specific clinical and pathological features (**Fig. 2B-C**).

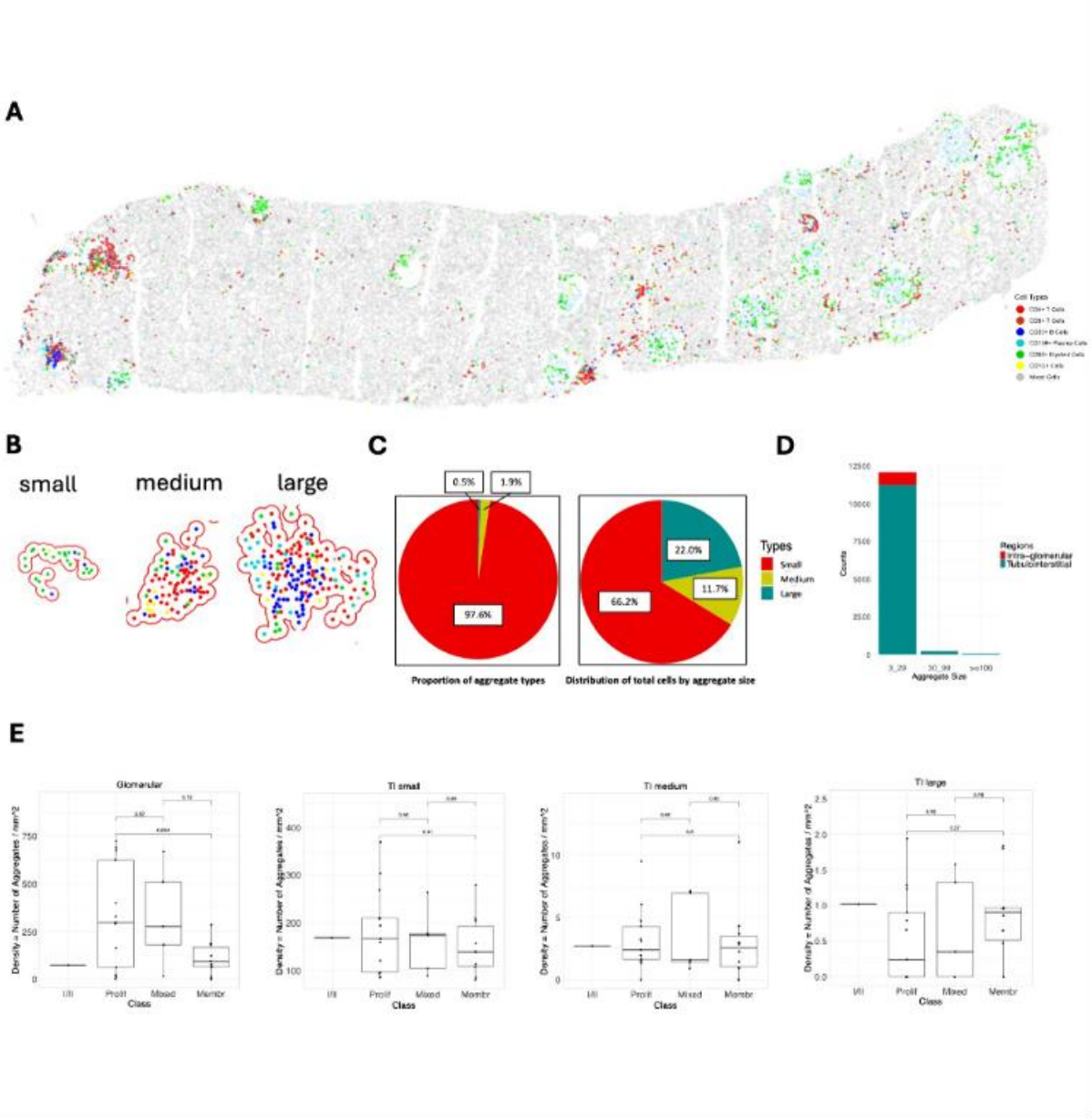


Figure 1. Demographics of intrarenal immune cell aggregates. (A) Digitalized biopsy showing an example of the distribution of immune cells in LN. (B) Examples of intrarenal immune cell aggregates of different sizes. (C) Distribution of aggregates by size and by total cells. (D) Distribution of aggregates by size and region. (E) Density of aggregate types according to size and
class.

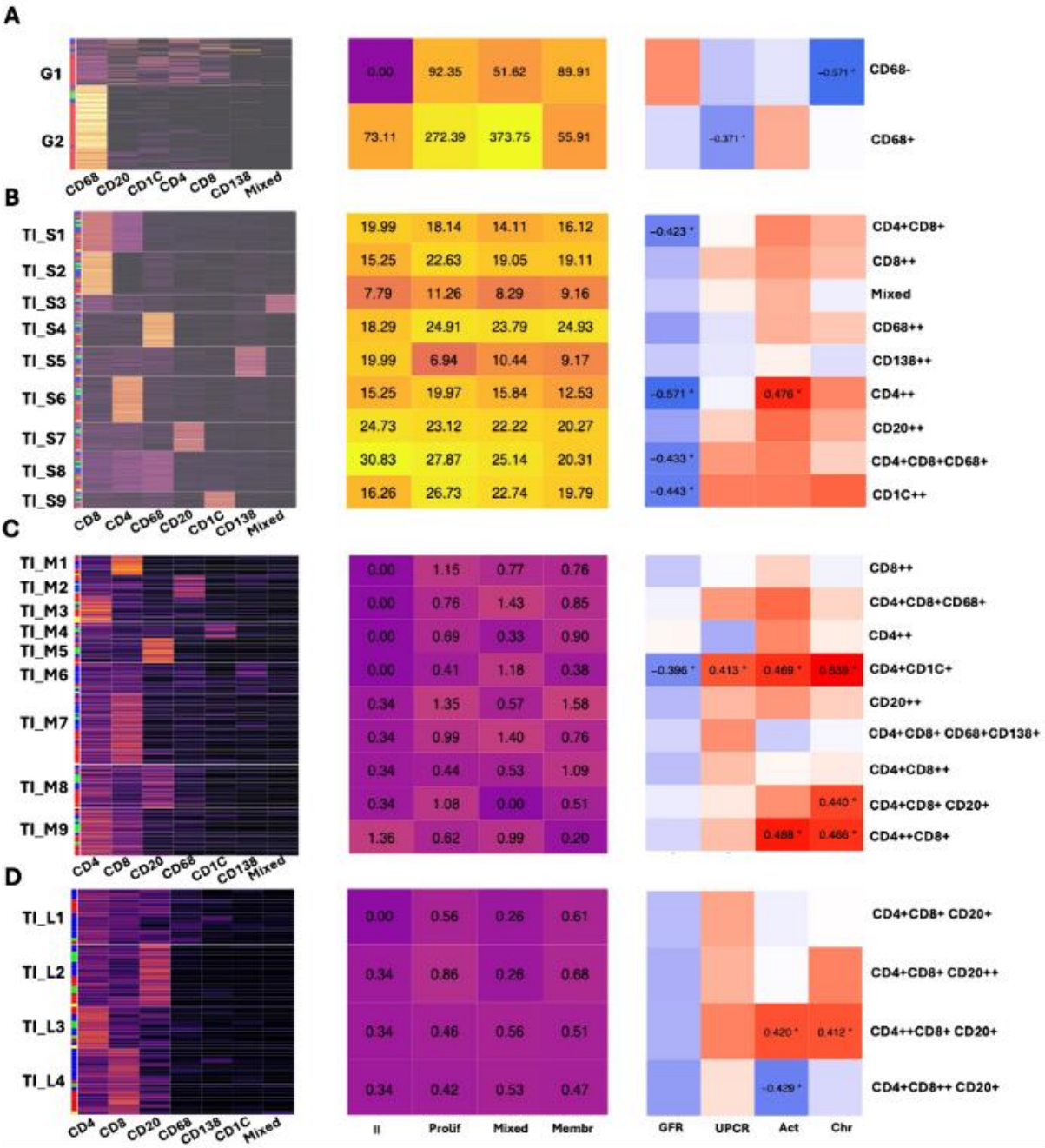


Figure 2. Correlation between aggregate subtypes and clinical features. Left heatmaps show aggregates subtypes. Middle heatmaps display the average density of aggregate subtypes (average number of aggregates/mm^2). Right heatmaps show the correlation matrices between the aggregate subtypes and clinical features. (A) Glomerular small aggregate (B) Tubulointerstitial small aggregate (C) Tubulointerstitial medium aggregate (D) Tubulointerstitial large aggregate. Act: NIH activity index; Chr: NIH chronicity index.

Conclusions: We describe the heterogeneity in glomerular and TI immune cell structures in LN, offering insights into LN pathological processes and potential cellular interactions based on proximity. TI inflammation appears similar in membranous and

proliferative LN, yet specific immune structures are linked to distinct clinical and pathological features.

O060 / #518

Topic: ***AS08 - Cytokines and Cell Trafficking***

ABSTRACT CONCURRENT SESSION 10: INTEGRATING PROTEOMIC & TRANSCRIPTOMICS IN SLE
24-05-2025 10:40 AM - 11:40 AM

INVESTIGATING PREDICTIVE SERUM SOLUBLE MEDIATORS SPECIFIC TO ANA+ INDIVIDUALS AT RISK OF SYSTEMIC LUPUS ERYTHEMATOSUS WITH HIGH-THROUGHPUT PROTEOMICS

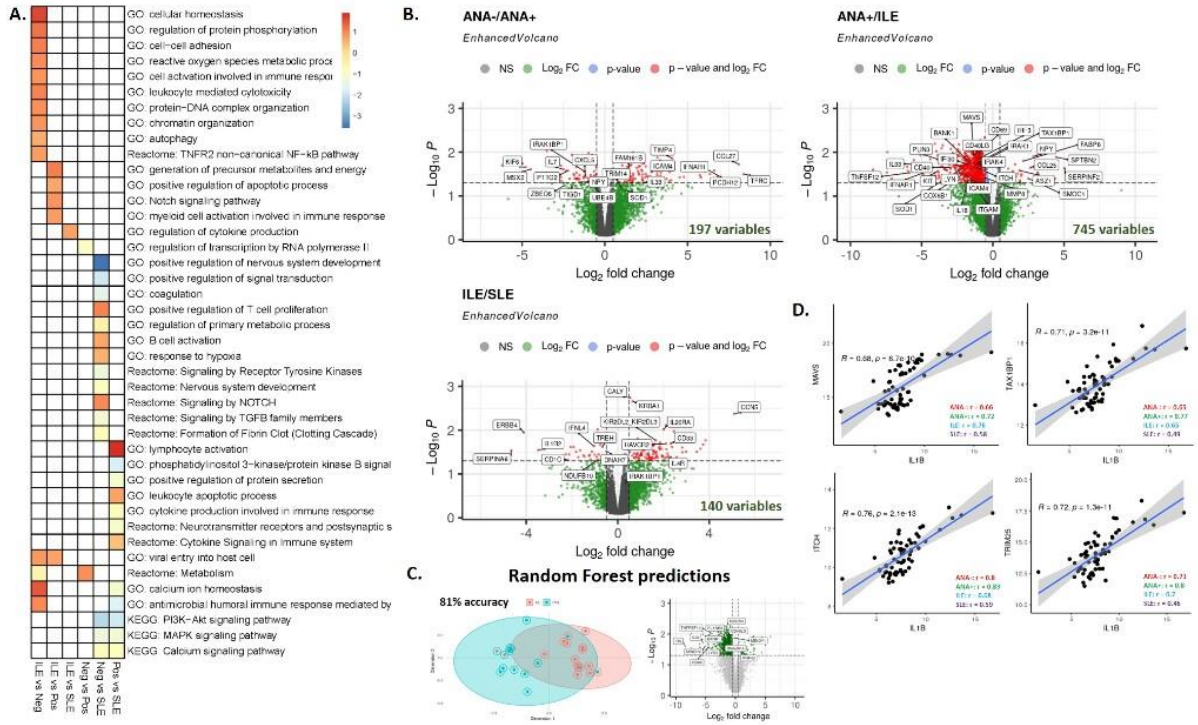
Aleksandra Bylinska, Miles Smith, Rufei Lu, Ben Jones, Carla Guthridge, Susan Macwana, Wade Dejager, Marci Beel, Judith James, Joel Guthridge
Oklahoma Medical Research Foundation, Oklahoma City, United States of America

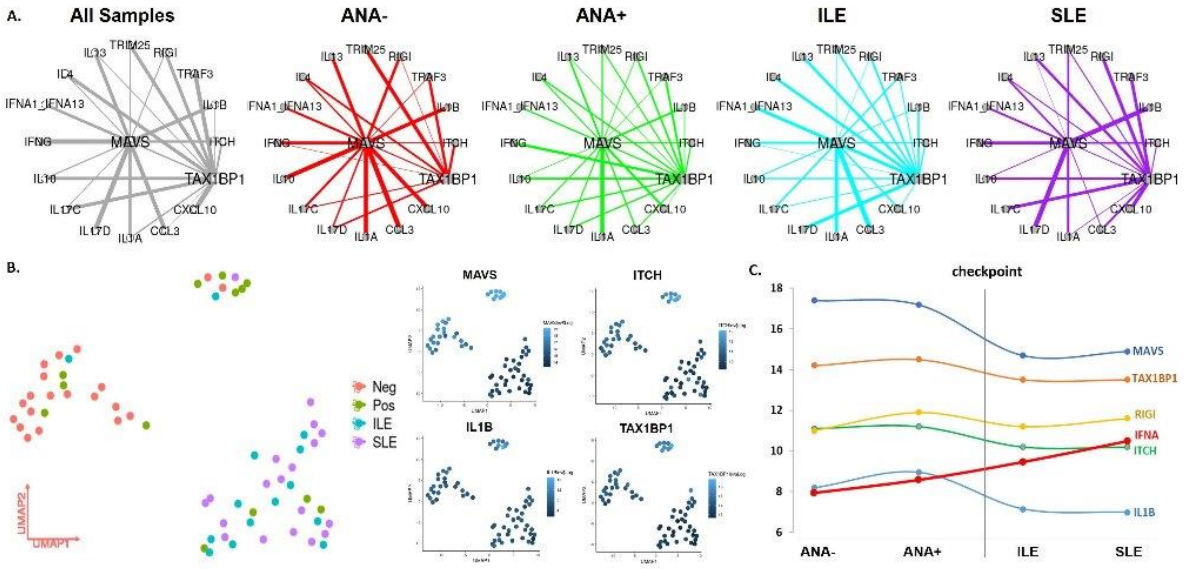
Background/Purpose: Anti-nuclear autoantibodies (ANAs) are detected years before SLE classification. However, most healthy ANA+ individuals will never develop clinical illness. Patients with incomplete lupus (ILE) exhibit some clinical symptoms with most never progressing to SLE. It is unknown what triggers ANA+ individuals to progress to clinical disease. We sought to identify molecular profiles of serum proteome driving transitions to full immune cell dysregulation.

Methods: Over 5400 proteins were measured in serum of 67 subjects (ANA-, ANA+ healthy; ILE; SLE) with Proximity Extension Assay (Olink Explore HT). Logistic regression with adjustment for age and genetic ancestry and machine learning approaches (Random Forest, GENIE3) were used to identify proteomic signatures specific for disease progression.

Results: Gene set enrichment analysis reveals involvement of pathways related to cellular homeostasis, lymphocyte activation, nucleic acid sensing, cytokine production and apoptosis. [Fig1a] Comparison of serum protein levels found the largest number of differences between ANA+ and ILE (745 proteins, p_{adj} <= 0.05), associated with upregulation (in ANA+) of ubiquitin related proteins (ITCH, TAX1BP1, TRIM25, UBE2L6, USP8, USP26, UBL4A, UBE2B, UBOX5), MAPK Signaling (MAP2K6, MAP3K5, MAPKAPK2, MAP7D2, MAPKAP1), pathways related to cell adhesion and cellular regulation (KIT, TGFB2, TNFRSF14, CD46, LGALS1, CD40, IL17D, IL33, TNFSF12) and mitochondrial proteins (MAVS). Significant proteins between ANA-/ANA+ healthy controls (197 proteins, p_{adj} <= 0.05) were related to decreased levels of IL7, transcription regulation pathways and increased cell adhesion molecules in ANA+. The lowest variability was found between ILE and SLE (140 proteins, p_{adj} <= 0.05) with increase of TNF, BANK1, IL33, IL4R. [Fig1b] Overall, random forest predictions indicate involvement of mitochondrial proteins, dysregulation of ubiquitin related pathways, Th2 Signaling and vesicular trafficking, specific to ANA+. [Fig1c] Mitochondrial and intracellular sensing

proteins, determined with above approaches, are associated with innate cytokine IL1B, mostly in early stages of disease progression. [Fig.1d] Inference of gene regulatory networks reveals interactions between pattern recognition proteins driven by mitochondrial MAVS, with variations in disease progression. Those interactions, as well as expression of related proteins, appear to be increased in ANA+, which might highlight MAVS as an initial mitochondrial modulator affecting regulation in early stages of disease. [Fig2a, b] Trajectory of pattern recognition proteins indicates increase in ANA+ and reduction in ILE and SLE, suggesting their potential role in regulating immune response before appearance of clinical symptoms. On the contrary, expression of IFN, CXCL10, IL6, IL10, IL13 gradually increase with disease progression, indicating importance of proinflammatory component during SLE development. [Fig2c]





Conclusions: Proteomic signatures specific to ANA+ are associated with disruption of cellular homeostasis and dysregulation of proteins related to pattern recognition, antiviral response and ubiquitination. These abnormalities may define important events in the trajectory of preclinical autoimmunity development.

O061 / #515

Topic: ***AS15 - Lupus Nephritis-Clinical***

ABSTRACT CONCURRENT SESSION 10: INTEGRATING PROTEOMIC & TRANSCRIPTOMICS IN SLE
24-05-2025 10:40 AM - 11:40 AM

PROTEOMIC ANALYSIS OF SERUM OVER TIME TO FORECAST TREATMENT RESPONSE IN LUPUS NEPHRITIS

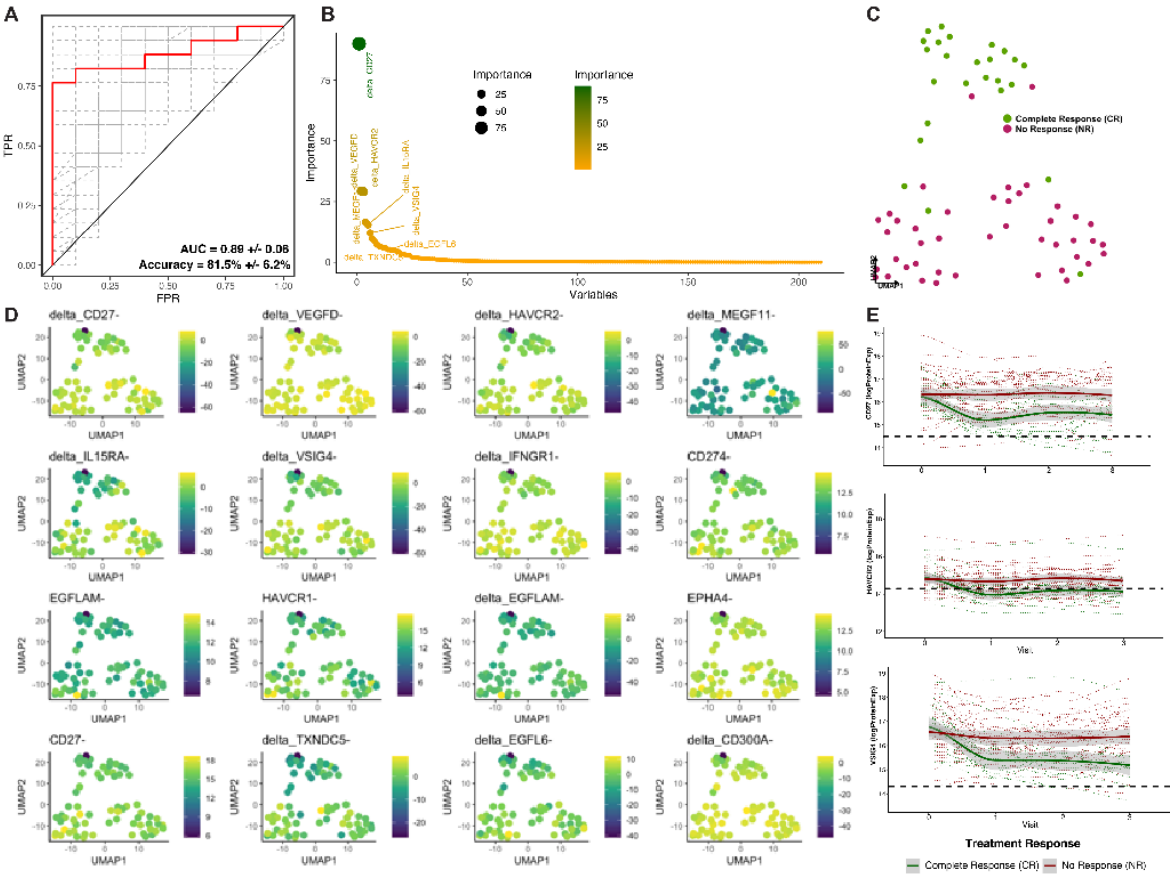
Rufei Lu[1], Andrea Fava[2], Peter Izmirly[3], Benjamin Jones[4], Jennifer Anolik[5], Chaim Putterman[6], David Wofsy[7], Diane L Kamen[8], Maria Dall'Era[9], Kenneth Kalunian[10], Michael H Belmont[3], Richard Furie[11], Susan Macwana[4], Wade Dejager[4], Catriona Wagner[1], E. Steve S. Woodle[12], Michael Weisman[13], Mariko Ishimori[14], Paul J. Utz[13], Betty Diamond[15], Jill Buyon[3], Michelle Petri[16], Judith James[4], Joel Guthridge[4]
[1]Oklahoma Medical Research Foundation, Arthritis And Clinical Immunology, Oklahoma City, United States of America, [2]John Hopkins University School of Medicine, Division of Rheumatology, Baltimore, United States of America, [3]New York University School of Medicine, Medicine, New York, United States of America, [4]Oklahoma Medical Research Foundation, Oklahoma City, United States of America, [5]University of Rochester Medical Center, Division Of Rheumatology, Rochester, United States of America, [6]Albert Einstein College of Medicine, Department Of Medicine, Bronx, United States of America, [7]University of California San Francisco, San Francisco, United States of America, [8]Medical University of South Carolina, Charleston, United States of America, [9]University of California San Francisco, Department Of Rheumatology, San Francisco, United States of America, [10]University of California, San Diego School of Medicine, Division Of Rheumatology, Autoimmunity And Inflammation, San Diego, United States of America, [11]Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Great Neck, United States of America, [12]University of Cincinnati College of Medicine, Cincinnati, United States of America, [13]Stanford University, Palo Alto, United States of America, [14]Cedars-Sinai Medical Center, Los Angeles, United States of America, [15]Institute of Molecular Medicine, Feinstein Institutes for Medical Research, Manhasset, United States of America, [16]John Hopkins University, Baltimore, United States of America

Background/Purpose: Lupus nephritis (LN) can cause severe complications and early mortality in SLE patients. Despite advancements, treatments for LN are not consistently effective and often have adverse effects. This study aims to develop a robust, non-invasive biomarker panel to predict treatment response, using high-throughput proteomics and machine learning to model serum protein expression, as part of the Accelerating Medicines Partnership RA/SLE Network.

Methods: Over 5,000 proteins were measured in the serum of 158 LN patients at the time of diagnostic kidney biopsy (baseline) and 12 weeks post-biopsy using Olink Explore HT. Clinical response was determined at 52 weeks as complete (CR; n=25), partial (PR; n=22), or no response (NR; n=49). Multivariate logistic regression adjusting for age, gender, and genetic ancestry and machine learning algorithm approaches (Extreme Gradient Boosting) were used to generate a robust prediction model of treatment responsiveness.

Results: At baseline, patients with NR exhibited 515 (p-value < 0.05; 160 upregulated) dysregulated proteins within the innate immune system, platelet activation, and pathways seen in neurodegeneration compared to CR. In addition, 1227 (p-value < 0.05; 1180 upregulated) proteins involving the TGFb, IL-10, Th1/Th2 differentiation, platelet activation, and leukocyte transendothelial migration pathways at 12 weeks post-biopsy were differentially expressed in patients with NR compared to CR. Proteins involved in T cell proliferation, Th17 cell differentiation, and TNF, Wnt, EGFR, and IL-10 signaling were persistently elevated at week 12 in NR compared to CR using paired analysis. The proteomic profiles of CR and NR are easily distinguishable at 52 weeks (AUC, 0.85 ± 0.10 with cross-validation accuracy of 76.1% ± 10.2%). While the ML models at baseline and 12 weeks showed less robust prediction performance with 65.9% ± 7.6% and 70.4% ± 7.3% (Figure 1 A-C), the model that incorporates the baseline protein levels and the changes from baseline to 12 weeks post-treatment showed the most robust prediction with AUC of 0.89 ± 0.06 and accuracy of 81.5% ± 6.2%. In particular, patients with a CR had a significant reduction in CD27, VEGF, HAVCR2, MEGF11, and VSIG4 from baseline to 12 weeks post-biopsy (Figure 1 D-E). Furthermore, preliminary trajectory analyses have demonstrated the rapid decline of these proteins before treatment with the levels plateauing near the levels seen in healthy controls throughout the 52-week of study trial. Gene regulatory network analyses of the top predictors demonstrated significantly down-regulated lymphocyte activation/differentiation (CD27, IL-7, IL-3, IL-16, CD83, and IL-10) and cellular migration pathways (NRP1, IL-16, PDGFB, CSF1, DDR1, FSTL1) in patients with a CR at week 12.

Conclusions: Early downregulation of specific immune pathways upon treatment precedes future clinical response in LN. Changes in serum protein expression, especially the soluble surface receptors shed upon cellular activation, at 12 weeks post-biopsy may serve as noninvasive biomarkers of 52-week treatment response.


A
TPR
FPR
AUC = 0.89 +/- 0.06
Accuracy = 81.5% +/- 6.2%
B
Importance
Variables
Importance
25
50
75
delta_CD27-
delta_VEGFD-
delta_HAVCR2-
delta_IL15RA-
delta_VSIG4-
C
Complete Response (CR)
No Response (NR)
UMAP1
UMAP2
D
delta_CD27-
delta_VEGFD-
delta_HAVCR2-
delta_MEGF11-
delta_IL15RA-
delta_VSIG4-
delta_IFNGR1-
CD274-
EGFLAM-
HAVCR1-
delta_EGFLAM-
EPHA4-
CD27-
delta_TXNDC5-
delta_EGFL6-
delta_CD300A-
E
Visit
Treatment Response
Complete Response (CR)
No Response (NR)

O062 / #591

Topic: ***AS24 - SLE-Treatment***

ABSTRACT CONCURRENT SESSION 10: INTEGRATING PROTEOMIC & TRANSCRIPTOMICS IN SLE
24-05-2025 10:40 AM - 11:40 AM

PREEXISTING ANTIBODIES AGAINST VACCINE ANTIGENS ARE PRESERVED IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS AND SJÖGREN'S DISEASE UPON IANALUMAB TREATMENT WHILE AUTOANTIBODIES DECLINE

Thomas Dörner[1], Nan Shen[2], Thomas Grader-Beck[3], Caroline Walter[4], Catherine Wioland[4], Celine Rauld[4], Patrick Schmutz[4], Simone Riek[4], Wolfgang Hueber[5], Carole Sips[4], Stephen Oliver[5], Carol Lau[6], Claire Bonal[4], Isabelle Isnardi[4]
[1]Department of Medicine, Rheumatology and Clinical Immunology, Charité Universitätsmedizin and Deutsches Rheumaforschungszentrum, Berlin, Germany, [2]Shanghai Institute of Rheumatology, Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China, [3]Division of Rheumatology, Johns Hopkins School of Medicine, Baltimore, United States of America, [4]Biomedical Research, Novartis Pharma AG, Basel, Switzerland, [5]Novartis Pharma AG, Basel, Switzerland, [6]Novartis Pharmaceuticals Corporation, East Hanover, United States of America

Background/Purpose: Ianalumab, an afucosylated monoclonal antibody, depletes B cells through enhanced antibody-dependent cellular cytotoxicity with concurrent blockade of B cell-activating factor (BAFF):BAFF-receptor (BAFF-R) mediated signals [1]. It is currently being investigated for the treatment of immune-mediated diseases. Given its novel mechanism of action, it is crucial to assess the effects of ianalumab on preexisting antibodies against vaccine antigens. Herein, we evaluated the impact of ianalumab treatment versus placebo on preexisting antibody levels against 7 pathogens in patients with systemic lupus erythematosus (SLE) and Sjögren's disease (SjD).

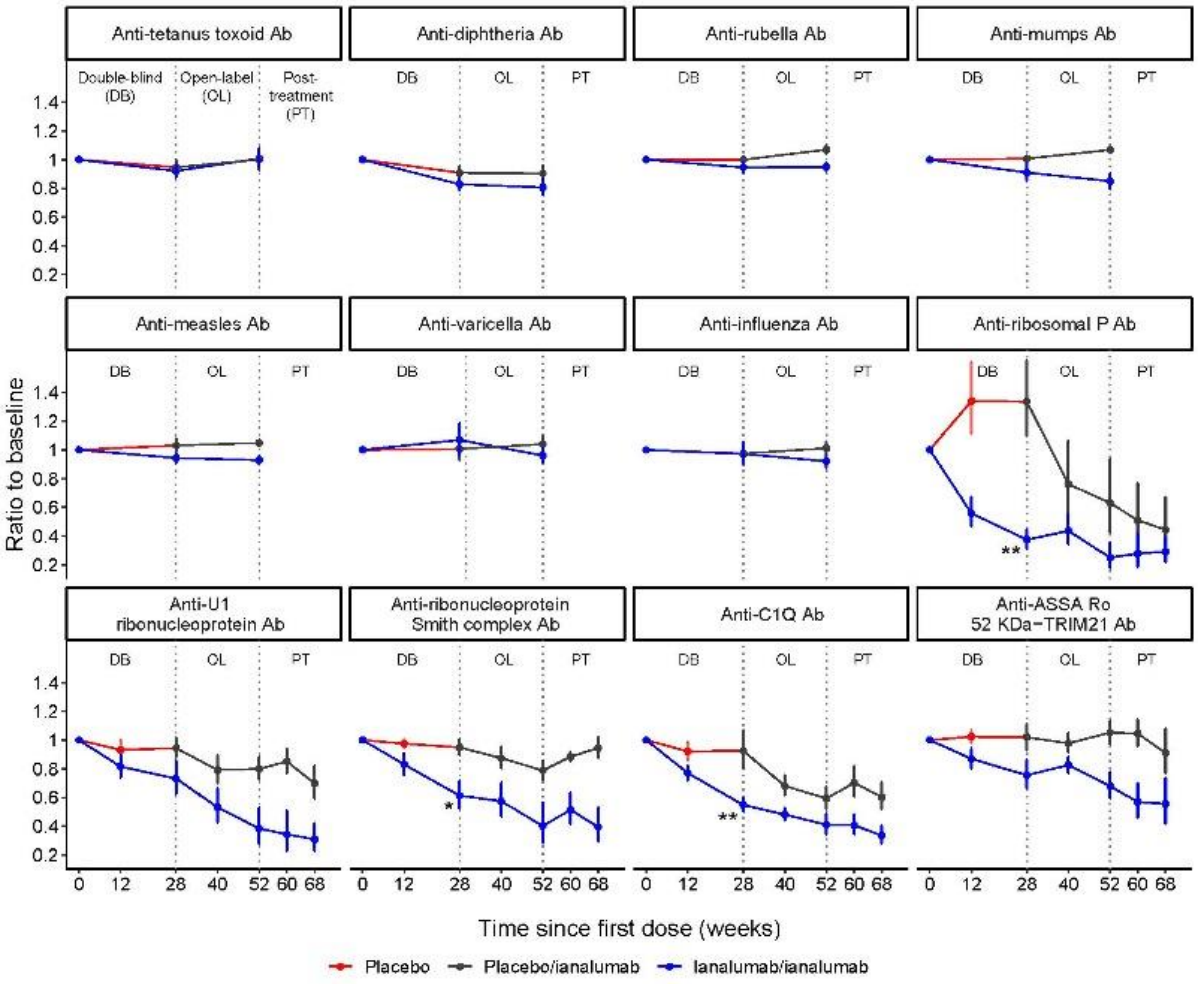
Methods: A retrospective analysis was conducted on serum samples from 2 randomized, double-blind, placebo-controlled phase 2 studies in patients with SjD (NCT02962895) or SLE (NCT03656562). Patients received either placebo or ianalumab 300 mg subcutaneous monthly for 24 weeks (79 patients with SjD) or for 28 weeks (40 patients with SLE). In the SjD study, patients on 300 mg ianalumab at Week 24 (W24) were re-randomized to receive double-blinded monthly ianalumab 300 mg or placebo until W52. Patients on placebo at W24 were switched to a lower ianalumab dose and were not subject to further testing in this analysis. In the SLE study, all patients switched from double-blind to open-label ianalumab up to W52. Antibodies (IgG isotypes) to vaccine antigens and autoantibodies were measured at baseline, W24 (SjD) or W28 (SLE) and W52. Changes in antibody levels from baseline and proportions of patients

maintaining protective levels at W52 were assessed. A total of 3 patients (2 SjD and 1 SLE) received booster doses against diphtheria and tetanus toxoid (TTd) under ianalumab treatment.

Results: The proportion of patients with SjD and SLE maintaining protective levels of antibodies against TTd, measles, mumps, varicella, rubella, diphtheria and influenza remained stable after ianalumab treatment up to 52 weeks. In patients with SjD, the changes from baseline to W24 were <6% for all antigens in both ianalumab- and placebo-treated patients. In patients with SLE, the changes from baseline to W28 were <10% in both ianalumab- and placebo-treated patients for all antigens besides diphtheria (**Figure 1**). For diphtheria, up to 18% changes were observed under ianalumab treatment, likely due to the low level of preexisting protection (<50% of patients had protective levels at baseline). In contrast, several auto-antibodies showed a significant reduction in ianalumab-treated patients (e.g. up to 60% reduction of anti-ribosomal P antibodies at W28) compared to placebo (**Figure 1**). These results are in line with the ability of ianalumab to deplete memory and antibody-producing cells [2], while likely not affecting the long-lived bone marrow plasma cells that do not express BAFF-R [3]. Among the 3 patients who received booster dose(s) against diphtheria and TTd during ianalumab treatment, 2 showed a subsequent increase in corresponding titers, whereas the other patient received the booster only 10 days before W52 sampling, likely explaining the lack of increased titers.

Conclusions: Treatment with ianalumab up to 52 weeks did not result in a reduction of the antibody titers to previous immunizations against tetanus, varicella, measles, mumps, rubella, diphtheria, and influenza while having a clear impact on autoantibody levels. **References:** 1. McWilliams EM, et al. *Blood Adv* 2019;3(3):447-460. 2. Dörner T, et al. *Ann Rheum Dis* 2024;83:956-957. 3. Darce JR, et al. *J Immunol* 2007;179 (11):7276-7286.

Figure 1. Titers from vaccine antigens and auto-antibody titers following treatment with ianalumab or placebo over time in patients with SLE.
Ratio to baseline of antibodies to vaccine antigens and autoantibodies were measured over time in patients with SLE treated with placebo vs ianalumab. All antibodies measured were IgG.



Significance values were calculated at the end of the double-blind period (28 weeks). *P<0.05; **P<0.01.
Ab, antibody; IgG, immunoglobulin G; SLE, systemic lupus erythematosus.

O063 / #228

Topic: ***AS21 - Pregnancy and Reproductive Health***

ABSTRACT CONCURRENT SESSION 11: PREGNANCY IN SLE
24-05-2025 10:40 AM - 11:40 AM

SAFETY OF FERTILITY TREATMENTS IN WOMEN WITH SYSTEMIC LUPUS ERYTHEMATOSUS: DATA FROM A FRENCH PROSPECTIVE POPULATION BASED STUDY.

Amandine Dernoncourt[1], Gaelle Guettrot-Imbert[2], Loïc Sentilhes[3], Marie-Charlotte Besse[4], Anna Molto[5], Viviane Queyrel-Moranne[6], Maelle Le Besnerais[7], Estibaliz Lazaro[8], Nathalie Tieulié[9], Christophe Richez[10], Eric Hachulla[11], Françoise Sarrot-Reynauld[12], Gaelle Leroux[13], Pauline Orquevaux[14], Jonathan London[15], Laurent Sailler[16], Odile Souchaud-Debouverie[17], Perrine Smets[18], Bertrand Godeau[19], Emmanuelle Pannier[20], Anne Murarasu[4], Alice Berezne[21], Tiphaine Goulenok[22], Nathalie Morel[23], Luc Mouthon[23], Pierre Duhaut[24], Véronique Le Guern[23], Nathalie Costedoat-Chalumeau[23]

[1]Centre Hospitalier Universitaire Amiens-Picardie, Service De Médecine Interne, Amiens, France, [2]Centre de référence des maladies auto-immunes et auto-inflammatoires systémiques rares d'Ile-de-France, de l'Est et de l'Ouest, Hôpital Cochin, Assistance Publique-Hôpitaux de Paris (AP-HP), Service De Médecine Interne, Paris, France, [3]Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France, [4]Centre Hospitalier Régional Universitaire de Tours, Tours, France, [5]AP-HP Hôpital Cochin, Paris, France, [6]Centre Hospitalier Universitaire de Nice, nice, France, [7]Centre Hospitalier Universitaire de Rouen, Rouen, France, [8]Hôpital du Haut-Lévêque, Centre Hospitalier Universitaire de Bordeaux, Centre de référence des maladies auto-immunes et auto-inflammatoires systémiques rares de l'Est et du Sud-Ouest, France., Bordeaux, France, [9]Centre Hospitalier Universitaire de Nice, Nice, France, [10]Centre Hospitalier Universitaire de Bordeaux, Centre de référence des maladies auto-immunes et auto-inflammatoires systémiques rares de l'Est et du Sud-Ouest, Bordeaux, France., Bordeaux, France, [11]Centre Hospitalier Universitaire de Lille, Service de Médecine Interne et Immunologie Clinique, Centre de référence des Maladies Auto-Immunes et Auto-inflammatoires Systémiques rares de l'Adulte du Nord, Nord-Ouest, Méditerranée et Guadeloupe (CeRAINOM), Lille, France, [12]Centre Hospitalier Universitaire Grenoble Alpes, grenoble, France, [13]AP-HP Hôpital Pitié-Salpêtrière, Paris, France, [14]Hôpital Robert Debré, Centre Hospitalier Universitaire de Reims, Reims, France, [15]Groupe Hospitalier Diaconesses Hôpital La Croix Saint-Simon, Paris, Paris, France, [16]Centre Hospitalier Universitaire de Toulouse, Toulouse, France, [17]Centre Hospitalier Universitaire de Poitiers, Poitiers, France, [18]Centre Hospitalier Universitaire de Clermont-Ferrand, Clermont-Ferrand, France, [19]AP-HP Hôpital Henri-Mondor, Paris, France, [20]Maternité Port-Royal, Hôpital Cochin, Paris, France, [21]Centre Hospitalier

Annecy Genevois, Epagny Metz-Tessy, France, [22]AP-HP Hôpital Bichat Claude Bernard, Paris, France, [23]Hôpital Cochin, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France, [24]CHU Amiens Picardie, Amiens, France

Background/Purpose: Fertility treatments, which involve the use of exogenous sex hormones, raise concerns about their safety in women with systemic lupus erythematosus (SLE).

Methods: This study included all pregnancies in women with SLE enrolled in the multicenter French prospective GR2 (Groupe de Recherche sur la Grossesse et les Maladies Rares, Clinicaltrial: NCT02450396) study, conceived before 1st August 2022, with available end-of-pregnancy data and known conception type [1]. Pregnancies were classified into two groups: those conceived naturally and those with assisted conception. Adverse pregnancy outcomes (APOs) were defined as the occurrence of an intrauterine fetal death after 12 weeks of gestation (WG), a placental insufficiency leading to preterm delivery before 37 WG, a small for gestational age, and/or a neonatal death [1,2]. Maternal flares were defined according to the SELENA-SLEDAI Flare Index. The main endpoint was the birth of a living child. Logistic regression was performed to assess whether fertility treatments were independently associated with live birth. Cumulative incidences of disease flares and APOs were also compared using Kaplan-Meier analysis (Cox regression model adjustment).

Results: 630 pregnancies met eligibility criteria, including 577 pregnancies obtained naturally in 478 women and 53 pregnancies through assisted conception (2 ovulation inductions, 12 intrauterine inseminations, and 39 in vitro fertilizations (IVF)) in 48 women. The mean age of women was older (35.8 vs. 32.3 years, $p < 1.10^{-4}$), and twins were more frequent in assisted pregnancies (5/50, 10.0% vs. 20/554, 3.6%; $p = 0.047$). Lupus disease was clinically inactive at baseline in 51/53 (96.2%) assisted pregnancies (vs 511/570, 89.6%; $p = 0.15$), with 10 of 45 (22.2%) having chronic damage (vs 65/513, 12.7%; $p = 0.07$). Lupus anticoagulant (LA) was present in 4/52 (7.7%) assisted pregnancies (vs 72/572, 12.6%; $p = 0.38$). Hydroxychloroquine was prescribed in 52/53 (98.1%) assisted pregnancies (vs 561/577, 97.2%; $p = 1.0$). About half of assisted and natural pregnancies (25/48, 52.1% vs 272/522, 52.1%; $p = 1.0$) were exposed to corticosteroids, but the daily prednisone dosage at inclusion was significantly higher in assisted pregnancies (median dose of 9 [IQR 5.0-10.0] vs. 5 [IQR 5.0-10.0] mg/day; $p = 0.025$). The live birth rate was similar between assisted and spontaneous pregnancies (46/53, 86.8% vs 505/577, 87.5%; $p = 0.83$). Assisted conception was not independently associated with achieving a live birth after adjusting for age, number of fetuses, gravidity, disease activity, damage, positive LA, exposure to low-dose aspirin, and daily prednisone dosage at inclusion (adjusted OR = 1.41 (95% CI 0.44-4.47), $p = 0.56$). At least one flare occurred in 9/53 (17.0%) assisted pregnancies (vs 96/565, 17.0%; $p = 0.74$). Among pregnancies progressing beyond 12 WG, at least one APO was reported in

8/48 (16.7%) assisted pregnancies (vs 86/525, 16.4%; $p = 0.98$). Cumulative incidences of flares, and APOs did not differ significantly between both groups. Fertility treatments did not appear to be an independent predictor of the occurrence of flare or APO after adjustment for confounding factors. When the analyses were limited to the group of pregnancies achieved by IVF, results remained unchanged.

Conclusions: Fertility treatments in women with mostly well-controlled SLE did not appear to increase risks of maternal and neonatal complications, supporting current recommendations [3].

References:

1. Larosa M, Le Guern V, Guettrot-Imbert G, Morel N, Abisror N, Morati-Hafsaoui C, et al. Evaluation of lupus anticoagulant, damage, and remission as predictors of pregnancy complications in lupus women: the French GR2 study. Rheumatol Oxf Engl. 2022;keab943.

2. Buyon JP, Kim MY, Guerra MM, Laskin CA, Petri M, Lockshin MD, et al. Predictors of Pregnancy Outcomes in Patients With Lupus: A Cohort Study. Ann Intern Med. 2015;163:153-63.

3. Sammaritano LR, Bermas BL, Chakravarty EE, Chambers C, Clowse MEB, Lockshin MD, et al. 2020 American College of Rheumatology Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases. Arthritis Rheumatol Hoboken NJ. 2020;72:529-56.

O064 / #405

Topic: ***AS21 - Pregnancy and Reproductive Health***

ABSTRACT CONCURRENT SESSION 11: PREGNANCY IN SLE
24-05-2025 10:40 AM - 11:40 AM

SUBOPTIMAL MEDICATION USE AND WORSE PERIPARTUM OUTCOMES IN WOMEN WITH LUPUS COMPARED TO THE GENERAL POPULATION

Stephanie Keeling[1], Anamaria Savu[2], Luan Chu[2], Padmaja Kaul[2]
[1]University of Alberta, Medicine, Edmonton, Canada, [2]University of Alberta, 2-132 Li Ka Shing Centre For Health Research Innovation, Edmonton, Canada

Background/Purpose: Observational and population levels studies confirm that systemic lupus erythematous (SLE) is associated with worse maternal and neonatal outcomes by way of disease activity and peripartum treatment choices compared to the general population without immune-mediated inflammatory diseases (IMID). [1]. Increasingly, international societies have modifed their recommendations for peripartum medication use and have recognized the general safety of medications such as hydroxychloroquine and azathioprine throughout pregnancy. [2]. We hypothesize that despite increased availability of safe peripartum disease treatments for SLE, outcomes are still worse and treatments underutilized compared to those without IMID in a contemporary Albertan pregnancy cohort

Methods: A contemporary pregnancy cohort of 446,017 women and corresponding birth events was assembled for the province of Alberta, Canada from the random selection of 1 live birth event per woman between Jan 1st, 2009 and December 31, 2023. We identified one group with no IMID (n=728,102) and one group with SLE (n=393) using ICD 9 and 10 codes and excluding mothers in the "no IMID" group with any dispensation of corticosteroids for 4 weeks or more during pregnancy. We compared maternal and neonatal outcomes, comorbid conditions and medication use at any point in the pregnancies amongst the two groups. Anatomical Therapeutic Chemical Classification System (ATC codes) were used to identify medication use during the 270 days prior to delivery.

Results: More SLE mothers (22.1%) were > 35 years old compared to 15.2% of no IMID mothers. Emergent and elective cesarean section deliveries were higher in women with SLE compared to those no IMID. Women with SLE were more likely to have preterm delivery (13.7%), “small for gestational age” babies (19.3%), and NICU admissions (18.6%), compared to those without IMID ([Table 1). Medication use amongst SLE mothers at any point in the pregnancy included 12.5% on glucocorticoids, 3.6% on non-steroidal anti-inflammatories, 25.4% on anti-malarials, 3.6% on non-biologic disease

modifying antirheumatic drugs and 1.3% on biologic DMARDs. No women had exposure to anifrolumab or belimumab.

Table 1. Maternal Characteristics and Peripartum Outcomes

Variable	No IMID	SLE
Total N	728,102	393
Age at delivery (year) Mean (SD)	30.0 (5.3)	32.1 (4.7)
>35 years # (%)	110,636 (15.2)	87 (22.1)
Ethnicity Chinese South Asian General population	3.2% 3.8% 93%	4.6% 5.6% 89.8%
Urban Residence # (%)	110,636 (15.2)	87 (22.1)
Multiparous # (%)	434,639 (59.7)	228 (58.0)
Emergent C-section delivery (%)	124,879 (17.2)	82 (20.9)
Elective C-section	85,730 (11.8)	59 (15.0)
Induction	232, 147 (31.9)	133 (33.8)
Preterm Birth	49,572 (6.8)	54 (13.7)
Small for Gestational Age # (%)	71, 196 (9.8)	76 (19.3)
NICU admission at birth # (%)	68,711 (9.4)	73 (18.6)

Conclusions: Women with SLE have worse peripartum outcomes compared to those without IMIDs. Medications such as anti-malarials which are safe in pregnancy are underutilized which may influence these outcomes. Further peripartum studies in this population are needed to evaluate drug uptake and safety over time and whether guidelines are impacting how clinicians manage these complex patients. REFERENCES: [1.] Tan Y. J Autoimmun 2022;132:102864. [2.] Russell M et al. Rheumatol (Oxford) 2023;62(4):1370-1387.

O065 / #407

Topic: ***AS18 - Paediatric SLE***

ABSTRACT CONCURRENT SESSION 11: PREGNANCY IN SLE
24-05-2025 10:40 AM - 11:40 AM

CHILDHOOD ONSET SYSTEMIC LUPUS ERYTHEMATOSUS: PREGNANCY AND BIRTH OUTCOMES IN ONTARIO

Zunaira Mehmood[1], Kuan Liu[2], Roberta Berard[3], Wesley Fidler[4], Janet Pope[5], Carter Thorne[6], Andrea Knight[7], Linda Hiraki[8], Earl Silverman[9], Deborah Levy[10]
[1]Dalla Lana School of Public Health, University of Toronto, Division Of Biostatistics, Toronto, Canada, [2]Dalla Lana School of Public Health, University of Toronto, Institute For Health Policy, Management, And Evaluation (ihpme) And Division Of Biostatistics, Toronto, Canada, [3]Children's Hospital, London Health Sciences Center, Division Of Paediatric Rheumatology, London, Canada, [4]Northern Ontario School of Medicine, Thunder Bay, Canada, [5]Western University, Divisions Of Rheumatology, Epidemiology, And Biostatistics, Department Of Medicine, London, Canada, [6]Centre of Arthritis Excellence (CaRE), Newmarket, Canada, [7]Neurosciences and Mental Health Program, SickKids Research Institute; Division of Rheumatology, The Hospital for Sick Children, Toronto, Canada, [8]Division of Rheumatology, The Hospital for Sick Children; Genetics and Genome Biology, SickKids Research Institute, Toronto, Canada, [9]The Hospital for Sick Children, Division Of Rheumatology, Toronto, Canada, [10]Division of Rheumatology, The Hospital for Sick Children; Child Health Evaluative Sciences, SickKids Research Institute, Toronto, Canada

Background/Purpose: Childhood onset systemic lupus erythematosus (cSLE) is a chronic, multi-system, autoimmune disease. Pregnancy and birth outcomes of women diagnosed with cSLE are not well understood. Long term follow-up of cSLE patients is required as patients transition from pediatric to adult rheumatology care. This present study uses a large province-wide cSLE cohort linked with multiple health administrative databases following cSLE patients from the time they were diagnosed (under 18 years old) into adulthood. Our objectives were to describe and evaluate pregnancy, neonatal, and maternal outcomes among females diagnosed with cSLE in Ontario; and to identify demographic and disease characteristics associated with adverse pregnancy and birth outcomes.

Methods: A population-based retrospective cohort study linked clinical data for eligible female patients diagnosed with cSLE between January 1985 and March 2011 and followed for ≥ 1 year from date of diagnosis to March 31, 2023 with multiple health administrative datasets housed at the Institute for Clinical Evaluative Sciences (ICES). We examined descriptive summaries of pregnancy, neonatal, and maternal outcomes. The primary outcome was fetal death (encompassing stillbirth, miscarriage, and

abortion). Secondary outcomes included preterm birth, neonatal hospitalization and morbidity, and various maternal outcomes (Table 1). We used unadjusted and adjusted Generalized Estimating Equations (GEE) to estimate the association between study outcomes and demographic and early disease characteristics. Specifically, we adjusted for age at diagnosis, years since cSLE diagnosis, ethnicity, income, anti-dsDNA antibodies, and biopsy-proven lupus nephritis. Using GEE enabled us to account for within-mother clustering from additional pregnancies during the follow-up period.

Results: Our study included 489 female cSLE patients diagnosed with cSLE between 1985 - 2011 and followed for 16.8 ± 7.2 years (mean ± SD). A total of 423 pregnancies occurred in 175 women during the follow-up period. 131 (75%) women had at least one live birth while 44 (25%) had no live births. 195 (46%) pregnancies resulted in fetal death, 73 (32.0%) of live births were preterm, and 76 (33%) of neonates were admitted to neonatal intensive care (Table 1). Our adjusted analysis (Table 2) shows that patients who were older at time of cSLE diagnosis have lower odds of fetal death (OR 0.87; 95% CI 0.78-0.97). Our univariate analyses show that odds of preterm birth are higher for patients with non-white ethnicity (OR 2.43; 95% CI 1.22–4.85), anti-Sm antibodies (OR 2.82; 95% CI 1.43–5.56), and biopsy-proven lupus nephritis (OR 2.51; 95% CI 1.27–4.98).

Conclusions: Investigating pregnancy, neonatal, and maternal outcomes is crucial for enhancing patient care and health resource management for cSLE patients. Age at diagnosis, non-white ethnicity, and early disease characteristics including anti-Sm antibodies, and biopsy-proven lupus nephritis are significantly associated with adverse pregnancy and birth
outcomes.

Table 1: Pregnancy, neonatal, and maternal outcomes among female cSLE patients		
Pregnancy Outcomes[a]	**Number of patients n (% of total)**	**Number of events n (% of total)**
Total	175	423
Live birth	131 (74.9)	228 (53.9)
Fetal Death	44 (25.1)	195 (46.1)
Stillbirth	8 (4.6)	8 (1.9)
Miscarriage	57 (32.6)	72 (17.0)
Abortion	68 (38.9)	115 (27.2)
Neonatal Outcomes[b]		
Total	131	228
Preterm birth	56 (42.8)	73 (32.0)
<28 weeks	11 (8.4)	17 (7.5)
28-35 weeks	18 (13.7)	23 (10.1)
36+ weeks	29 (22.1)	33 (14.5)
Requiring NICU admission	54 (41.2)	76 (33.3)
Neonatal morbidity	58 (44.3)	76 (33.3)
Infections	6 (4.6)	9 (3.9)
Respiratory & cardiovascular disorders	29 (22.1)	38 (16.7)
Hemorrhagic & hematological disorders	28 (21.4)	35 (15.4)
Endocrine & metabolic disorders	22 (16.8)	30 (13.2)
Digestive system and other disorders	18 (13.7)	22 (9.7)
Adverse Maternal Outcomes[a]		
Total	175	423
Pre-eclampsia or Eclampsia	28 (16.0)	36 (8.5)
Hypertension	36 (20.6)	49 (11.6)
Thrombosis & embolism	10 (5.7)	13 (3.1)
Cesarian sections	19 (10.9)	22 (5.2)
Postpartum infection	9 (5.1)	10 (2.4)
Diabetes mellitus	11 (6.3)	14 (3.3)
Note: Proportions are calculated as: (a) percent of all events (fetal deaths and live births) for pregnancy and maternal outcomes, (b) percent of all live births for neonatal outcomes.		

Table 2: Adjusted Analysis Model for Fetal Death		
Parameter	**OR Estimate**	**95% CI**
Years since diagnosis	0.871	[0.829, 0.915]
Age at diagnosis (in years)	0.867	[0.776, 0.969]
Ethnicity is non-white (vs. white)	1.597	[0.965, 2.643]
High income (vs. low/middle income)	1.139	[0.642, 2.021]
Anti-dsDNA	1.483	[0.831, 2.645]
Renal involvement	1.151	[0.640, 2.068]
Note: Binary outcome is fetal death (=1 if pregnancy results in stillbirth, miscarriage, or abortion, =0 if pregnancy results in live birth).		

O066 / #230

Topic: ***AS21 - Pregnancy and Reproductive Health***

ABSTRACT CONCURRENT SESSION 11: PREGNANCY IN SLE
24-05-2025 10:40 AM - 11:40 AM

OVERWEIGHT AND OBESITY ARE KEY MODIFIABLE RISK FACTORS FOR ADVERSE OUTCOMES IN SLE PREGNANCIES

Evelyne Vinet[1,2], Ann Clarke[3], Megan Barber[3], Paul R Fortin[4], John Hanly[5], Alexandra Legge[5], Sang-Cheol Bae[6], Karim Sacre[7], Sasha Bernatsky[1,8]
[1]McGill University Health Centre, Medicine, Divisions Of Rheumatology And Clinical Epidemiology, Montreal, Canada, [2]Research Institute of the McGill University Health Centre, Centre For Outcomes Research And Evaluation (core), Montreal, Canada, [3]University of Calgary, Division Of Rheumatology, Cumming School Of Medicine, Calgary, Canada, [4]Universite Laval, Centre Arthrite - Chu De Québec, Quebec City, Canada, [5]Dalhousie University, Medicine, Halifax, Canada, [6]Hanyang University Hospital for Rheumatic Diseases, Rheumatology, Seoul, Korea, Republic of, [7]Université de Paris, Rheumatology, Paris, France, [8]Research Institute of McGill University Health Centre, Centre For Outcomes Research And Evaluation (core), Montreal, Canada

Background/Purpose: High maternal body mass index (BMI) is a well-established modifiable risk factor for adverse pregnancy outcomes (APO) in the general obstetric population. Best practices recommend appropriate pre-pregnancy weight management to optimize outcomes. However, the prevalence of obesity and its impact in systemic lupus erythematosus (SLE) pregnancies are poorly understood, despite the higher APO risk in SLE. We evaluated baseline BMI in a prospective SLE pregnancy cohort to determine if overweight (25-29.9 kg/m^2) or obese (≥30 kg/m^2) BMI conferred higher APO risk compared to BMI < 25 kg/m^2

Methods: We enrolled pregnant SLE women at <17 weeks gestation at Systemic Lupus International Collaborating Clinics (SLICC) centres in Canada (Montreal, Quebec City, Calgary, Halifax) and South Korea (Seoul). We collected data on demographics, obstetrical history, SLE characteristics, baseline co-morbidities, and APO at each of the 2nd trimester, 3rd trimester, and end-of-pregnancy visits (8-12 weeks after end of pregnancy). APO included 1) fetal death >20 weeks gestation, 2) neonatal death due to preterm birth and/or placental insufficiency, 3) preterm delivery or termination < 36 weeks due to placental insufficiency, gestational hypertension, preeclampsia, and/or eclampsia, and 4) small for gestational age (SGA; < 5th percentile). We assessed the proportion of APO across the different BMI groups. We conducted a multivariate analysis using the Korean BMI classification for pregnancies from Asian mothers, categorizing BMI as follows: obese (BMI ≥25), overweight (BMI 23-24.9), and normal weight (BMI < 23).

Results: We analyzed 80 completed pregnancies, with a mean maternal age of 33.9 years (standard deviation, SD 4.1) and a mean maternal BMI of 26.0 kg/m^2 (SD 6.7). Almost half (40%) of pregnancies had a maternal BMI ≥25 kg/m^2. Non-Hispanic Whites made up 40% of the pregnancies and more than half (56%) of pregnancies with a maternal BMI ≥30 kg/m^2 (Table 1). Aspirin use was more common in the BMI ≥30 kg/m^2 group, while steroids were more frequently used in pregnancies with BMI < 25 kg/m^2. Overall, APO occurred in 8 (10%) pregnancies (Table 2). The proportion of APO was 19% [95% confidence interval (CI) 0, 38%] in both the BMI 25-29.9 kg/m^2 and BMI ≥30 kg/m^2 groups and 4% (95% CI 1, 12%) in the BMI < 25 kg/m^2 group. In univariate analysis, there was more than a 5-fold increased risk of APO in pregnancies with maternal BMI ≥25 kg/m^2 versus those with BMI < 25 kg/m^2 [odds ratio (OR) 5.31; 95% CI 1.00, 28.24]. In multivariate analysis, using the Korean BMI classification for all Asian mothers, as well as adjusting for race and antiphospholipid antibody status, overweight and obese pregnancies had a substantially increased risk of APO compared to those with normal weight (OR 6.32; 95% CI 1.25, 32.0).

Conclusions: Overweight and obese SLE women had a higher risk of APO compared to the normal weight group. High BMI may be a modifiable risk factor for APO in women with SLE. Preconception weight interventions may improve outcomes in SLE pregnancies. Table1. SLE Pregnancy Characteristics by Body Mass Index (BMI, kg/m2)

Characteristics	Overall (n=80)	BMI ≥30 (n=16)	BMI 25-29.9 (n=16)	BMI <25 (n=48)
Demographics				
Age, mean (SD)	33.9 (4.1)	33.4 (3.9)	34.8 (3.8)	33.7 (4.2)
BMI, mean (SD)	26.0 (6.7)	37.1 (5.8)	27.3 (1.2)	21.8 (2.1)
Race/Ethnicity, n (%) Non-Hispanic White	32 (40.0)	9 (56.3)	7 (43.8)	16 (33.3)
Obstetrical History				
Gravidity, mean (SD)	2.5 (1.7)	3.1 (2.1)	2.8 (1.5)	2.2 (1.5)
Previous fetal death ≥10 weeks, n (%)	3 (3.8)	1 (6.3)	2 (12.5)	0 (0)
Previous premature births <34 weeks, n (%)	5 (6.3)	3 (18.8)	0 (0)	1 (2.1)
SLE Characteristics				
SLE Pregnancy Disease Activity Index, mean (SD)	1.9 (2.5)	2.2 (2.8)	1.8 (2.2)	1.9 (2.6)
Prior and/or current nephritis, n (%)	27 (33.8)	2 (12.5)	4 (25.0)	21 (43.8)
Antiphospholipid antibody, n (%)† Positive	19 (23.8)	4 (25.0)	5 (31.3)	10 (20.8)
Lupus anticoagulant, n (%) Positive	12 (15.0)	3 (18.8)	5 (31.3)	4 (8.3)
Co-morbidities				
Diabetes, n (%)	3 (3.8)	2 (12.5)	1 (6.3)	0 (0)
Hypertension, n (%)	4 (5.0)	3 (18.8)	0 (0)	1 (2.1)
Current Medications				
Aspirin, n (%)	51 (63.8)	13 (81.3)	10 (62.5)	28 (58.3)
Oral steroids, n (%)	17 (21.3)	3 (18.8)	2 (12.5)	12 (25.0)
Antimalarials, n (%)	72 (90.0)	14 (87.5)	13 (81.3	45 (93.8)
Immunosuppressives, n (%)	33 (41.3)	9 (56.3)	6 (37.5)	18 (37.5)
† n=1 pregnancy with BMI <25 with missing antiphospholipid antibody status				

Table 2. Pregnancies with Adverse Outcomes by Body Mass Index (BMI, kg/m2)

Adverse Pregnancy Outcomes (APO)	Overall (n=80)	BMI ≥30 (n=16)	BMI 25-29.9 (n=16)	BMI <25 (n=48)
Pregnancies with any APO, n (%)	8 (10.0)	3 (18.8)	3 (18.8)	2 (4.2)
Fetal death >20 weeks, n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Neonatal death due to preterm birth and/or placental insufficiency, n (%)	2 (2.5)	0 (0)	1 (6.3)	1 (2.1)
Preterm delivery or termination <36 weeks[†], n (%)	5 (6.3)	2 (12.5)	2 (12.5)	1 (2.1)
Small for gestational age (birth weight <5th percentile), n (%)	4 (5.0)	2 (12.5)	2 (12.5)	0 (0)
[†] Due to placental insufficiency, gestational hypertension, preeclampsia, or eclampsia				

O067 / #277

Topic: ***AS21 - Pregnancy and Reproductive Health***

ABSTRACT CONCURRENT SESSION 11: PREGNANCY IN SLE
24-05-2025 10:40 AM - 11:40 AM

IMPACT OF CHILDCARE ON PATIENT REPORTED OUTCOME IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS: A CROSS-SECTIONAL STUDY FROM THE LUPUS REGISTRY OF NATIONWIDE INSTITUTION (LUNA) COHORT

Dai Kishida[1], Takanori Ichikawa[1], Yasuhiro Shimojima[1], Nobuyuki Yajima[2,3], Ken-Ei Sada[4,5], Yoshia Miyawaki[5], Yoshimi Ryusuke[6], Shigeru Ohno[7], Kunihiro Ichinose[8,9], Toshimasa Shimizu[9], Shuzo Sato[10], Hiroshi Kajiyama[11], Michio Fujiwara[12], Takashi Kida[13], Yusuke Matsuo[14], Keisuke Nishimura[15], Yoshiki Sekijima[1]
[1]Shinshu University School of Medicine, Department Of Medicine (neurology And Rheumatology), Matsumoto, Japan, [2]Division of Rheumatology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan, [3]Center for Innovative Research for Communities and Clinical Excellence, Fukushima Medical University, Fukushima, Japan, [4]Department of Clinical Epidemiology, Kochi Medical School, Kochi University, Nankoku, Japan, [5]Department of Nephrology, Rheumatology, Endocrinology and Metabolism, Okayama University Graduate School of Medicine, Okayama, Japan, [6]Department of Stem Cell and Immune Regulation,Yokohama City University Graduate School of Medicine, Yokohama, Japan, [7]Center for Rheumatic Diseases, Yokohama City University Medical Center, Yokohama, Japan, [8]Department of Rheumatology, Shimane University Faculty of Medicine, Shimane, Japan, [9]Department of Immunology and Rheumatology, Division of Advanced Preventive Medical Sciences, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [10]Fukushima Medical University School of Medicine, Department of Rheumatology, Fukushima, Japan, [11]Department of Rheumatology and Applied Immunology Faculty of Medicine, Saitama Medical University, Iruma, Japan, [12]Department of Rheumatology, Yokohama Rosai Hospital, Yokohama, Japan, [13]Inflammation and Immunology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan, [14]Department of Rheumatology, Tokyo Kyosai Hospital, Tokyo, Japan, [15]Department of Rheumatology and Clinical Immunology, Kobe University Graduate School of Medicine, Kobe, Japan

Background/Purpose: Systemic lupus erythematosus (SLE) often develops at a young age leading to concerns regarding pregnancy, childbirth, and childcare. Although recent advances in treatment have increased safety during childbirth, the situation of patients with SLE raising children alongside their treatment is unknown. The quality of life (QOL) in healthy individuals tends to decline from the postpartum to the parenting period. However, the burden of parenting may be greater in patients with SLE than in healthy

individuals because of perinatal relapse and child-rearing difficulties due to fatigue and functional impairment. In this study, we examined the impact of childcare on the QOL of patients with SLE.

Methods: This cross-sectional study used data from a multicenter SLE registry, the lupus registry of nationwide institution (LUNA). We excluded female patients with a confirmed parenting status, those within 8 weeks postpartum, those with cancer, and those whose child's age could not be confirmed. First, to evaluate the impact of childcare on patients' QOL during treatment, the exposure was parenting, divided into two categories (including infants aged 0–5 years and only schoolchildren aged 6–18 years), and patients who developed SLE during childcare were excluded. Next, to evaluate the effect of the timing relationship between SLE onset and childcare, we restricted the analysis to patients who were raising children, with SLE onset during childcare as the exposure. The outcomes were QOL (HRQOL, non-HRQOL, and each domain of the Lupus PRO) in both analyses. Multiple regression analysis was performed using patient age, number of children, SLICC/ACR Damage Index, cohabitation with spouse, and caregiving as confounding factors. The missing values were complemented using multiple imputations.

Results: A total of 695 participants (mean age, 42.3 years, mean disease duration, 13.5 years) were included. Among them, 113 had SLE onset before childcare (67 with infants and 46 with schoolchildren only), 64 developed SLE during childcare (1 with infants and 63 with schoolchildren only), and 518 did not receive childcare. Patients who gave birth and raised infants during treatment showed significantly better cognition scores (memory and concentration) than those who were not performing childcare (regression coefficient 11.5, 95% CI 0.4–22.7, p=0.042). Patients who developed SLE while raising their children also had significantly higher social support scores than those who had the disease before starting childcare (regression coefficient 8.5, 95% CI 0.69–16.3, p=0.033).

Conclusions: The presence of an infant was associated with good cognitive function in patients with SLE who were raising children while undergoing treatment. In contrast, patients who developed SLE while raising their children received better support from their families and friends. Our findings may help reduce anxiety in patients with SLE regarding pregnancy, childbirth, and subsequent childcare.

O068 / #494

Topic: ***AS18 - Paediatric SLE***

ABSTRACT CONCURRENT SESSION 12: PEDIATRIC SLE – ADVANCES IN DISEASE OUTCOMES AND MENTAL HEALTH
24-05-2025 10:40 AM - 11:40 AM

EXAMINING THE RELATIONSHIP BETWEEN SOCIODEMOGRAPHIC FACTORS AND MENTAL HEALTH IN CHILDHOOD-ONSET SYSTEMIC LUPUS ERYTHEMATOSUS

Jasmine Jing[1], Andrea Knight[2], Ashley Danguecan[3], Linda Hiraki[4], Deborah Levy[5], Jida Jaffan[6], Asha Jeyanathan[1], Lawrence Ng[1], Paris Moaf[1], Joanna Law[7], Angela Cortes[8], Eugene Cortes[8], Sandra Williams-Reid[9], Kiah Reid[10]
[1]The Hospital for Sick Children, Rheumatology, Toronto, Canada, [2]Neurosciences and Mental Health Program, SickKids Research Institute; Division of Rheumatology, The Hospital for Sick Children, Toronto, Canada, [3]The Hospital for Sick Children, Psychology, Toronto, Canada, [4]Division of Rheumatology, The Hospital for Sick Children; Genetics and Genome Biology, SickKids Research Institute, Toronto, Canada, [5]Division of Rheumatology, The Hospital for Sick Children; Child Health Evaluative Sciences, SickKids Research Institute, Toronto, Canada, [6]The Hospital for Sick Children, Toronto, Canada, [7]Sunnybrook, North York, Canada, [8]SickKids, Toronto, Canada, [9]TTI Travel Canada, Toronto, Canada, [10]McMaster University, Hamilton, Canada

Background/Purpose: Childhood-onset systemic lupus erythematosus (cSLE) is a chronic autoimmune disease with significant adverse impact on mental health. Furthermore, patients with cSLE often face health disparities due to marginalization involving individual-level race and ethnicity, household-level and neighborhood-level socioeconomic factors. We aimed to understand the impact of these multi-level sociodemographic factors for marginalization on mental health in youth with cSLE.

Methods: We conducted a retrospective cross-sectional cohort study of publicly insured cSLE patients (9-18 years) recruited from an outpatient lupus clinic in Ontario, Canada from October 2017-December 2023. All patients met ACR or SLICC criteria for SLE classification. The exposure of marginalization included measures for individual race and ethnicity, household low-income status, and neighborhood level Ontario Marginalization Index (material resources, racialized and newcomer population dimensions). Mental health outcomes included the presence of clinically elevated anxiety symptoms, measured by the Screen for Childhood Anxiety Related Disorders (SCARED), and depression symptoms, measured by the Center for Epidemiologic Studies Depression Scale for Children (CES-DC) or Children's Depression Inventory/Beck Depression Inventory (CDI/BDI). Logistic regression models examined associations between the marginalization exposure variables and the mental health outcomes, adjusting for age, sex, disease duration and activity.

Results: 100 cSLE patients were included. Marginalization characteristics are shown in Figure 1. 27% of the cohort lived in low-income households, and 52% lived in areas with the highest density of racialized and newcomer populations. Symptoms for anxiety were present in 43% and depression in 40%. Patients living in the most marginalized quintile of neighborhood material resources had higher odds of depressive symptoms compared to those in more material resourced neighborhoods (OR=4.2, 95% CI 1.2-13.9, p=0.02, Table 1). No other significant associations were observed for depressive symptoms, and no associations were found for anxiety symptoms.

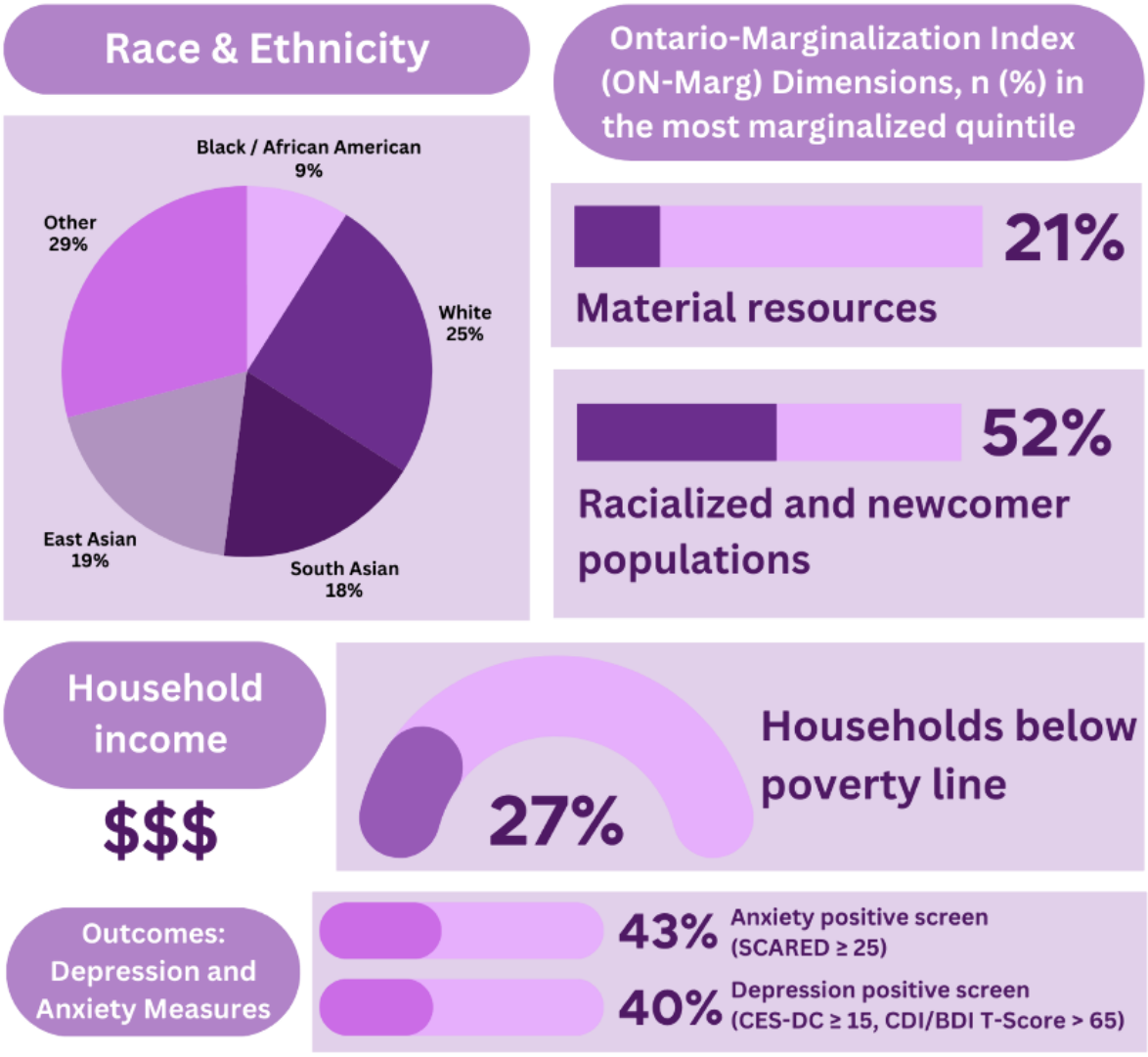


Table 2: Multivariable Logistic Regression Model for Association between Marginalization, Depression, and Anxiety Symptoms		
Marginalization Exposure Variables		
Race and Ethnicity	Depression: Odds Ratio (95% CI), p-value	Anxiety: Odds Ratio (95% CI), p-value
White (reference)	-	-
Black	0.397 (0.062, 2.544), p=0.330	0.251 (0.041, 1.55), p=0.137
East Asian	0.898 (0.207, 3.901), p=0.886	0.741 (0.184, 2.98), p=0.672
South Asian	1.227 (0.274, 5.501), p=0.789	0.713 (0.167, 3.04), p=0.647
Other	1.201 (0.310, 4.644), p=0.791	0.881 (0.247, 3.15), p=0.846
Low household income status		
No (reference)	-	-
Yes	2.676 (0.930, 7.703), p=0.068	2.333 (0.834, 6.53), p=0.106
ON Marg - material resources - most marginalized quintile		
No/quintiles 1-4 (reference)	-	-
Yes/quintile 5	4.152 (1.242, 13.88), p=0.021	2.192 (0.675, 7.12), p=0.192
ON Marg – racialized and newcoming populations - most marginalized quintile		
No/quintiles 1-4 (reference)	-	-
Yes/quintile 5	0.745 (0.257, 2.16), p=0.588	1.171 (0.415, 3.30), p=0.766
Covariates		
Age	1.226 (0.936, 1.604), p=0.139	1.092 (0.855, 1.39), p=0.482
Sex		
Female (reference)	-	-
Male	0.641 (0.136, 3.018), p=0.574	0.401 (0.089, 1.81), p=0.235
Disease duration (months)	0.985 (0.968, 1.001), p=0.072	0.992 (0.977, 1.01), p=0.303
Disease activity (SLEDAI-2K>4)		
No (reference)	-	-
Yes	0.894 (0.314, 2.543), p=0.833	0.369 (0.130, 1.05), p=0.062

Figure 1: Shown are marginalization characteristics and mental health outcomes for the cSLE cohort (n=100). The “Other” race and ethnic category included individuals identifying as Indigenous, Middle Eastern, Southeast Asian, Latin American or multi-ethnicity.

Conclusions: In a publicly insured Canadian cohort of youth with cSLE, we found that those living in neighborhoods with the lowest material resources were at highest risk for

depression symptoms. Further research into other social determinants of health is essential to improve mental health support for youth with cSLE from diverse socioeconomic backgrounds.

O069 / #96

Topic: ***AS18 - Paediatric SLE***

ABSTRACT CONCURRENT SESSION 12: PEDIATRIC SLE – ADVANCES IN DISEASE OUTCOMES AND MENTAL HEALTH
24-05-2025 10:40 AM - 11:40 AM

ADVERSE CHILDHOOD EXPERIENCES: PREVALENCE AND RELATIONSHIP TO DISEASE OUTCOMES IN CHILDHOOD-ONSET SYSTEMIC LUPUS ERYTHEMATOSUS (CSLE)

Jin Xuan Zhou[1,2,3], Stephanie Fevrier[2], Paris Moaf[2], Lawrence Ng[2], Asha Jeyanathan[2], Louise Boulard[2], Deborah Levy[2], Linda Hiraki[2], Ashley Danguecan[4], Andrea Knight[1]
[1]SickKids Research Institute, Neurosciences And Mental Health Program, Toronto, Canada, [2]The Hospital for Sick Children, Rheumatology, Toronto, Canada, [3]Queen's University, Faculty Of Health Sciences, Kingston, Canada, [4]The Hospital for Sick Children, Psychology, Toronto, Canada

Background/Purpose: Childhood-onset systemic lupus erythematosus (cSLE) is an autoimmune disease characterized by multi-organ inflammation, alongside high frequencies of mood disorders and cognitive impairment. Adverse Childhood Experiences (ACEs) quantify traumatic childhood events, which have been linked to altered immune response and increased chronic disease risk. Prior studies indicate that those with ≥ 4 ACEs, including adults with SLE, face higher risk of worse health outcomes. Limited research exists on ACEs in cSLE. We aimed to describe the prevalence of ACEs among cSLE patients and investigate associations with i) disease activity, ii) patient-reported outcome measures, and iii) self-reported executive function.

Methods: This cross-sectional study analyzed prospective data from cSLE patients aged 13-19 years at the time of assessment. The Pediatric ACEs and Related Life Events Screener (PEARLS) measured self-reported ACEs. Disease activity over the time since diagnosis was measured by the adjusted mean Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K). The Patient Reported Outcomes Information System (PROMIS) Pediatric-37 Profile assessed patient-reported anxiety, depression, and fatigue. The Behavior Rating Inventory of Executive Function (BRIEF-2) Global Executive Composite score measured executive function. The frequency of ACEs types was tabulated, and patients were classified into high-risk (≥ 4 ACEs) and low-risk (≤ 3 ACEs) groups. Associations between ACEs risk group and the outcomes were examined using regression analyses with generalized linear models, adjusted for age.

Results: Of 48 cSLE patients (mean age 15.23 ± 1.87 years, 85% female), 73% reported at least 1 ACE, and 30% reported ≥ 4 ACEs (Table 1). The most common ACEs were

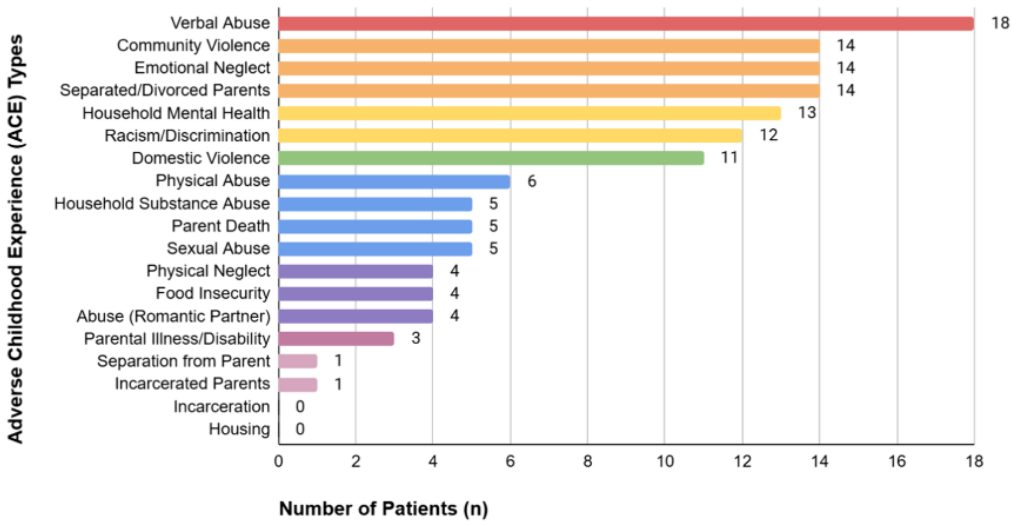
caregiver verbal abuse, emotional neglect, and separation, as well as community violence (Figure 1). Being in the high-risk ACEs group compared to low risk, was significantly associated with worse scores for PROMIS anxiety ($p<0.001$), depression ($p<0.001$), and fatigue ($p=0.001$), alongside poorer executive function scores ($p<0.001$) (Figure 2). No significant associations were observed for disease activity ($p=0.987$).

Conclusions: Within our cSLE cohort, ACEs were substantially prevalent, with almost a third of patients having experienced ≥ 4 ACEs. The high risk group (≥ 4 ACEs) had significantly worse patient-reported outcomes across anxiety, depression, fatigue, and executive function. These results underscore the impact of ACEs on patient well-being, emphasizing the need for integrated medical and mental health care approaches. Future research should examine these associations within larger cohorts. Table 1. Patient Demographics, Disease Characteristics, and Outcome Measures

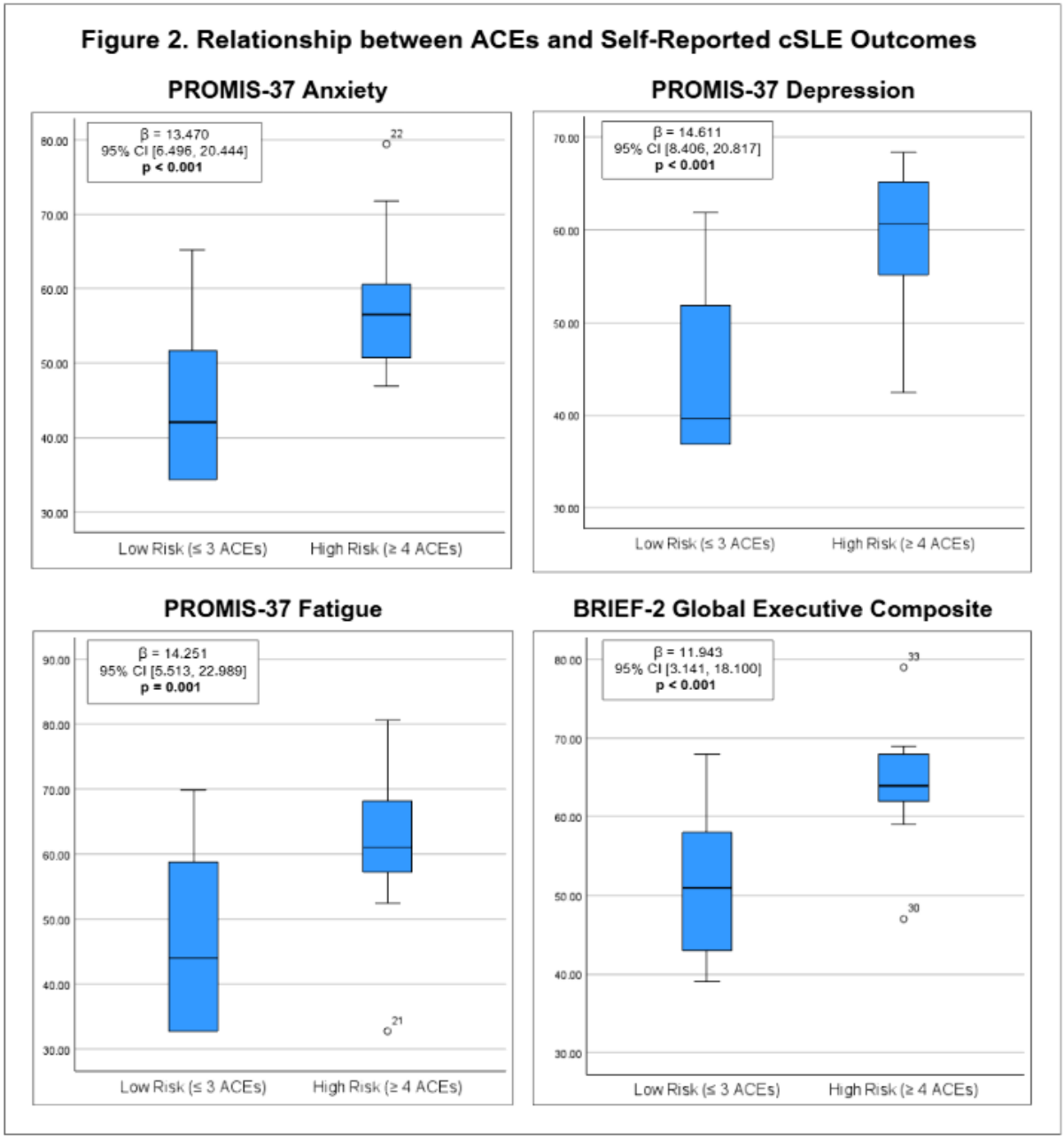
Table 1. Patient Demographics, Disease Characteristics, and Outcome Measures	cSLE Patient Cohort (n=48)
Demographic Characteristics	
Age in years, mean (SD)	15.2 (1.9)
Female, n (%)	41 (85)
Low-income families, n (%)	15 (31)
Race and Ethnicity, n (%)	
Asian	26 (54)
Black/African American	8 (17)
White	10 (21)
Other [a]	4 (8)
Self-Identified ACEs Presence (PEARLS), n (%)	
0 ACEs	13 (27)
1 - 3 ACEs	20 (42)
≥ 4 ACEs	15 (31)
Disease Characteristics	
Disease Duration in Years, median (IQR)	1.0 (0.6, 2.6)
Adjusted-mean SLEDAI-2K, median (IQR)	4.0 (2.5, 7.4)
Glucocorticoid use (ever), n (%)	35 (73)
Patient-Reported Outcome Measures (PROMIS-37), mean (SD)	
Fatigue [b]	50.3 (13.6)
Anxiety [b]	48.4 (11.3)
Depression [b]	48.1 (10.7)
Behavior Rating Inventory of Executive Function (BRIEF-2), mean (SD)	
Global Executive Composite [b]	54.5 (10.3)
Note. [a] Other categories include Latin American (n=3) and multiethnic (n=1) race and ethnicities [b] Measures are negatively-worded standardized t-scores with a normative mean of 50 and standard deviation of 10. A t-score of 60 indicates outcomes 1 SD worse than average.	

Figure 1. Self-Reported Adverse Childhood Experiences (ACEs) in Patients with cSLE: Frequency and Types

Figure 1. Self-Reported Adverse Childhood Experiences (ACEs) in Patients with cSLE: Frequency and Types



Note. **Figure 1 illustrates the distribution of nineteen reported adverse childhood experiences (ACEs) types within our cSLE cohort (n=48). Among the total ACEs (n=134) self-reported on the patient PEARLS questionnaire, the most commonly reported ACEs were caregiver verbal abuse (n=18), community violence (n=14), emotional neglect (n=14), and caregiver separation/divorce (n=14). Figure 2. Relationship between ACEs and Self-Reported cSLE Outcomes**



Note. **Figure 2 contains four sets of boxplots depicting differences in mean outcome scores between the high-risk and low-risk ACEs groups. Associations show beta coefficients, confidence intervals, and p-values from regression analyses. Regression analyses showed significant associations for worse PROMIS anxiety (p<0.001), depression (p<0.001), and fatigue (p=0.001) scores alongside poorer executive function (p<0.001) within the high-risk group. The p-value threshold used for significance was p<0.05. Acknowledgements: Lupus Research Alliance, U.S. Department of Defense**

O070 / #568

Topic: ***AS18 - Paediatric SLE***

ABSTRACT CONCURRENT SESSION 12: PEDIATRIC SLE – ADVANCES IN DISEASE OUTCOMES AND MENTAL HEALTH
24-05-2025 10:40 AM - 11:40 AM

INCIDENCE AND RISK FACTORS OF HERPES ZOSTER INFECTION IN PEDIATRIC SYSTEMIC LUPUS ERYTHEMATOSUS: A 16 YEAR STUDY

Adrienne Katrin Guiang-Valerio
University of Santo Tomas Hospital, Pediatric Rheumatology, Sampaloc, Manila, Philippines

Background/Purpose: Systemic lupus erythematosus (SLE) is a prototypic chronic multisystem autoimmune disease that is highly heterogenous in its clinical manifestations and severity. Although SLE predominantly affects young women, children and adolescents contribute to 15–20% of this population.[1] Herpes zoster is viral disease caused by reactivation of varicella-zoster virus which remains dormant in the sensory ganglia of the cranial nerve or the dorsal root ganglia after a previous varicella infection. There is limited information on the association of HZ and cSLE. This study aims to determine the risk factors of HZ infection in patients diagnosed with cSLE at a tertiary hospital in the Philippines.

Methods: This study is a single center retrospective cohort study which included all patients aged 18 years old and below at the time they were diagnosed with SLE between 2008 and 2023.

Results: A total of 388 patients were included in the study. The prevalence of herpes zoster was 15.72% (95% CI = 12.24% to 19.73%), with an incidence rate of 38.40 per 100 person-years (95% = 0.316 to 0.469). The median age at cSLE diagnosis was 13 years old (IQR = 11 – 16). Majority of the participants were females (92.78%) and had a median disease duration of 9 years (IQR = 5 – 12). The most common location of the HZ was the upper extremities (18.03%). The median SLEDAI at herpes zoster diagnosis was 4 (IQR = 0 – 12), 16.39% had recurrent HZI, 11.48% had superimposed bacterial infection, and more than two-thirds were treated with the anti-viral acyclovir or valacyclovir (88.52%). The proportion of participants with renal manifestations was significantly higher among those with herpes zoster infection (54.10% vs. 40.37%). Using multivariate analyses, glucocorticoid dosage ≥5mg (aRR=10.20, p=0.001), azathioprine (aRR=2.07, p=0.009), and intravenous cyclophosphamide (aRR=1.61, p=0.048) significantly predicted the likelihood of developed herpes zoster infection.

Conclusions: The prevalence and incidence of HZI in cSLE is 15.72% and 38.40 per 100 person-years, respectively. Risk factors identified for HZI among cSLE were lymphopenia, lupus nephritis, and immunosuppressive agents. In particular, IV cyclophosphamide, azathioprine, and glucocorticoid dose of ≥5mg increased the risk for development of HZI by 1.61, 2.07, 10.20 times, respectively.

O071 / #598

Topic: ***AS18 - Paediatric SLE***

ABSTRACT CONCURRENT SESSION 12: PEDIATRIC SLE – ADVANCES IN DISEASE OUTCOMES AND MENTAL HEALTH
24-05-2025 10:40 AM - 11:40 AM

PARTNERING WITH ADOLESCENTS AND YOUNG ADULTS WITH CHILDHOOD-ONSET LUPUS TO IMPROVE ENGAGEMENT IN CARE

Tamar Rubinstein[1,2,3], Claudia Lechuga[4], Avni Dave[4], Lisbel Guzman[2], Sheza Suleman[2], Yendaly Arias[5], Pancy Brown[5], Carlene Harrison[6], Melissa French[7], Bhumi Parikh[8], Yedida Teitelman[2], Chaim Putterman[9,10], Jonathan Alpert[3], Vilma Gabbay[3,11], Laurie Bauman[2]
[1]Children's Hospital at Montefiore, Pediatric Rheumatology, Bronx, United States of America, [2]Albert Einstein College of Medicine, Pediatrics, Bronx, United States of America, [3]Albert Einstein College of Medicine, Psychiatry & Behavioral Sciences, Bronx, United States of America, [4]Albert Einstein College of Medicine, Bronx, United States of America, [5]NA, Bronx, United States of America, [6]LupusChat, New York, United States of America, [7]Lupus Foundation of America, Washington, DC, United States of America, [8]Valera Health, Brooklyn, United States of America, [9]Albert Einstein College of Medicine, Department Of Medicine, Bronx, United States of America, [10]Azrieli Faculty of Medicine, Zefat, Israel, [11]University of Miami, Psychiatry & Behavioral Sciences, Coral Gables, United States of America

Background/Purpose: Adolescents and young adults (AYA) with lupus, particularly those in the Bronx, New York, face significant barriers to care, contributing to inconsistent medical care and poor outcomes. Mobile health (mHealth) apps have the potential to improve engagement in care and can be tools to provide informational and psychosocial support and improve access and communication with the clinical team. This project aimed to adapt an existing mHealth app for AYA with lupus to improve engagement in care with input from youth through a structured participatory process.

Methods: The adaptation process followed the ADAPT-ITT framework. An initial literature search was conducted to determine potential targets and methods to improve engagement in care for youth with lupus. This identified psychological barriers (mainly depression) and disease education as potential targets and mobile health apps as a potential method effective in this age group. Initial key-informant meetings with a lupus educator, two patients, a patient advocate, a project manager for a mHealth app company, and research staff established broad app functionalities and major educational topics. Semi-structured focus groups, termed "engagement studios," were conducted with AYA with lupus to explore preferences for content, delivery methods, and engagement strategies for the app's two primary functions: (1) educational support

and (2) communication with a rheumatology nurse. Feedback from these sessions informed iterative refinements. A beta version of the app was subsequently theater-tested for usability and user experience.

Results: Over the course of a year of key-informant meetings a proposal for the educational and the nurse communication components of an existing mHealth app (Valera Health) was developed. The educational component was organized around 6 major educational topics (understanding lupus, symptom management, medications, mental health, general health & wellness, and social/financial support). Articles were reviewed from the Lupus Foundation of America's National Resource Center on Lupus (funded by the Centers for Disease Control and Prevention) and sourced for material that covered the major topics and was thought to be appropriate and appealing to adolescents and young adults. To address the heterogeneity of disease the key-informant group determined that there should be "tracks" that users could choose from to customize educational material around particular needs. The proposal for the nurse communication function was organized around supporting users with visit and medication adherence and potential root barriers to care. Sixteen participants were recruited for the Engagement Studios, targeting AYA with a history of inconsistent lupus care. Through the Engagement Studios the educational component was refined to include three tracks (Lupus & Brain, Lupus & Kidneys, Lupus & Skin) with multi-media content to be sent to users and available through the app's imbedded library. Reproductive health was added as an educational topic (originally proposed by key-informants as its own track). It was determined that over a 6-month trial, users would be messaged twice a week, with an educational piece and then for nurse outreach. Nurse outreach would address visit/medication adherence and assist with three key barriers (social needs, mental health, and disease knowledge/health literacy) through planned messages and include ad-hoc bi-directional messaging. AYA participating in theater-testing confirmed general usability and valued personalization, concise delivery formats, and the availability of information from a trusted source.

Conclusions: Partnering with and eliciting feedback from AYA with lupus in the adaptation process ensured that the resulting mHealth tool addressed their unique needs and preferences. Future work will evaluate the app's effectiveness in improving engagement in care and clinical outcomes.

O072 / #800

Topic: *AS18 - Paediatric SLE*
Late-Breaking Abstract

ABSTRACT CONCURRENT SESSION 12: PEDIATRIC SLE – ADVANCES IN DISEASE OUTCOMES AND MENTAL HEALTH
24-05-2025 10:40 AM - 11:40 AM

IDENTIFYING HOMOGENOUS ENDOPHENOTYPES IN CHILDHOOD ONSET SLE WITH DATA DRIVEN METHODS

Nicholas Chan[1], Nicholas Gold[1], Anjali Jain[2], Deborah Levy[1], Andrea Knight[1], Earl Silverman[1], Lawrence Ng[1], Lauren Erdman[3], Linda Hiraki[1]
[1]The Hospital for Sick Children, Rheumatology, Toronto, Canada, [2]The Hospital for Sick Children, Genetics And Genome Biology, Toronto, Canada, [3]Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States of America

Background/Purpose: Childhood-onset Systemic Lupus Erythematosus (cSLE) is a clinically heterogeneous autoimmune disease. We hypothesized that data-driven methods would identify clinically homogeneous patient subgroups that may represent cSLE endotypes with distinct genetics.

Methods: We included patients diagnosed with cSLE between January 1992-October 2023. All patients met 2019 ACR-EULAR classification criteria and were genotyped on Illumina multiethnic arrays. Ungenotyped single nucleotide polymorphisms were imputed with TopMed as a referent. We extracted SLE manifestations, date of each manifestation onset and demographics from dedicated Lupus databases. Ancestry was genetically inferred using principal components and ADMIXTURE with 1000 Genomes as a referent. We used time from SLE diagnosis to each manifestation to identify patient clusters using similarity network fusion (SNF), a data-driven method. We used Kaplan Meier analyses and Cox proportional-hazard models to compare clusters. We tested cluster differences in demographic and manifestation prevalences using χ^2 or Fisher's exact test, and time to each SLE manifestation onset with log rank tests. Our clustering was validated with simulation-based sensitivity analysis (1000 iteration of simulated SNF). Each iteration randomly subsampled 70% of our cohort, performed SNF and tested cluster differences in demographics, manifestation prevalence and each SLE manifestation onset. Genetic studies tested 162 SLE associated genes from 3 trans-ancestral SLE genome wide association studies and 33 monogenic SLE genes with cluster membership using sequence kernel association tests (SKAT). SKAT was weighted by minor allele frequency and adjusted for sex, ancestry and age of diagnosis. The threshold for significance was adjusted for multiple comparison with the Bonferroni correction ($P < 2.6 \times 10^{-4}$; 0.05 / 195).

Results: Our cohort included 442 cSLE patients. 83% were female and the median age of SLE diagnosis was 13.6 years (Q1-Q3: 12.0-15.8). The majority of patients were of European (27%) and East Asian (26%) ancestry, followed by South Asian (18%), Admixed (17%) and African (12%) ancestry. SNF identified 2 clusters. Patients in cluster 1 (n = 205) were predominantly of European ancestry (42%), while cluster 2 (n = 237) was mainly composed of patients of East Asian (30%) and South Asian (22%) ancestry ($P = 3x10^{-9}$). Patients in cluster 2 had higher prevalence of class III/IV lupus nephritis, fever, oral ulcers, hypocomplementemia, anemia, leukopenia, anti-cardiolipin and anti-Smith antibodies compared to patients in cluster 1 ($P < 1x10^{-7}$; Figure 1). Moreover, patients in cluster 2 had an earlier onset of developing the same 9 SLE manifestations as the risk of developing each manifestation at any time was higher in cluster 2 compared to cluster 1 (HR > 1.4; $P < 4x10^{-3}$). Simulation-based sensitivity analysis demonstrated that the same 9 SLE manifestation consistently drove clustering (>900/1000 times) and 95% of patients consistently clustered together over 1000 simulations. None of the 195 SLE genes were associated with cluster membership.

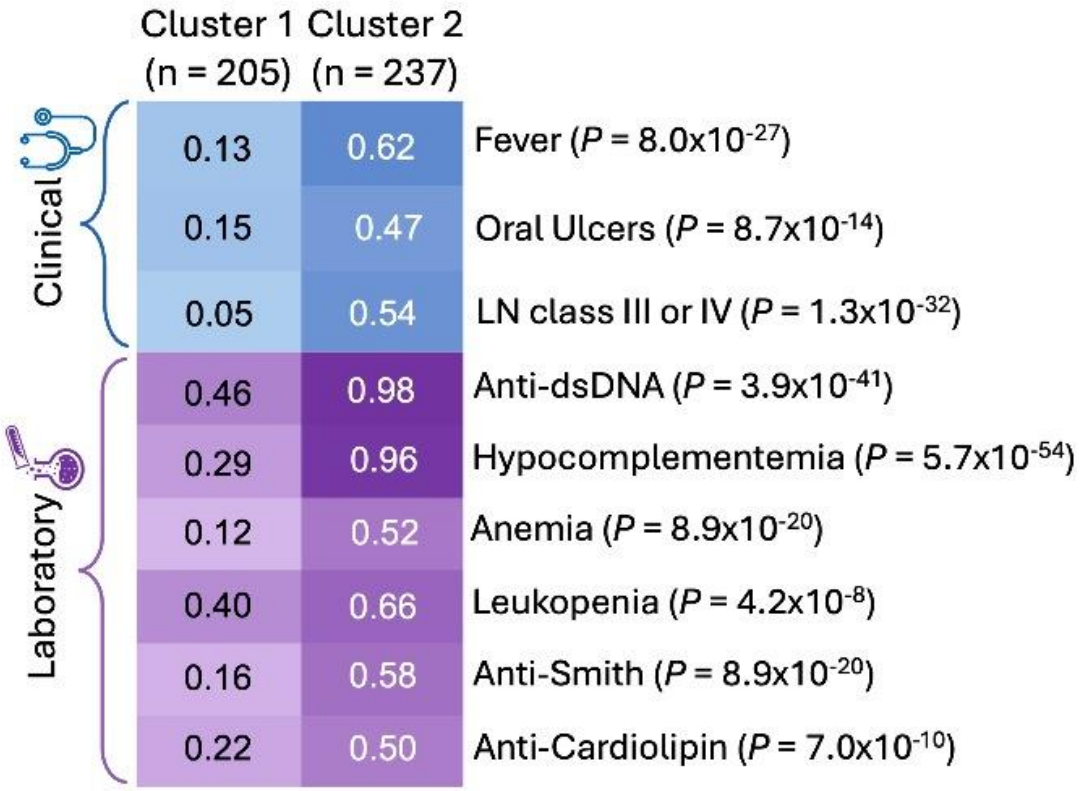


Figure 1: Clinical and Laboratory SLE Manifestation With Different Prevalences Between Patient Clusters. The number in each cell represents the prevalence of an SLE manifestation within cluster 1 and 2, respectively. "LN" stands for lupus nephritis. Statistics performed with a Fisher's Exact Test, Bonferroni corrected $P < 0.002$.

Conclusions: In a large multiethnic cSLE cohort, data-driven methods identified two robust cSLE patient clusters. The cluster with more severe disease and younger onset had a greater proportion of patients of East Asian and South Asian ancestry compared to the cluster with milder disease. Simulation-based sensitivity analysis demonstrated that 95% of patients consistently clustered together and 9 SLE manifestation primarily determined these clusters. Future work elucidating the role of genetics in our clustering is needed.