Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with heterogeneous clinical presentation and disease course. Therefore, the development of an instrument to measure SLE disease activity with high validity, reliability, responsiveness to change and feasibility is a major challenge. An optimal instrument with these properties should be practical to apply as a primary endpoint in clinical trials and in clinical practice to: assess in individual patients the severity of disease activity; assess the efficacy of medications and guide management decisions; and identify attainment of treatment targets and new SLE flares. Such an instrument would provide an operational tool to implement treat-to-target management of SLE patients in clinical practice and to optimize the design of clinical trials for new SLE treatments. This presentation aims to report most recent advances in the development of major disease activity measures and treatment target definitions to fulfill these clinical needs.

The SLE Disease Activity Index (SLEDAI), with 24 items, provides a global measure, it is practical to apply and extensively used in clinical practice and trials. However, it presents low sensitivity to change and does not include several important disease manifestations. The British Isles Lupus Assessment Group (BILAG) instrument is an organ-based measure that includes 97 items within nine organ-systems. It is more time-consuming to apply, thus not widely used in clinical practice. The Physician’s Global Assessment (PGA) uses a visual analogue scale for physicians to quantify SLE global activity in a 0–3 range. It is practical to apply, but its reliability is limited, due to a lack of standardisation.

Recognising the limitations of these instruments, composite responder indexes were developed (i.e. SLE Responder Index [SRI] and BILAG-Based Composite Lupus Assessment [BICLA]), by including the SLEDAI, BILAG and PGA, that are used as primary outcome measure in SLE clinical trials. However, the SRI and BICLA are not feasible in the clinical setting, and not appropriate to identify flares or treatment targets.

The treatment target for SLE patients is remission or, if that is not achievable, at least low disease activity (LDA), and this target should be maintained over time without flares and with a low dose of prednisone (or stopping them, when possible). Target definitions were developed using the SLEDAI as their basis (e.g., DORIS and LLDAS for remission and LDA, respectively), but require additional items for filling the gaps in the SLEDAI.

The SLE Disease Activity Score (SLE-DAS) is a recently validated 17-item instrument with continuous measurement properties for global SLE activity. It is quick to apply with its online calculator (http://sle-das.eu/). The SLE-DAS presents high accuracy in measuring SLE disease activity, high sensitivity-to-change, as well as higher predictive value for damage accrual as compared to SLEDAI-2K. The SLE-DAS provides validated, accurate and easy-to-apply definitions for categories of disease activity, and for the treatment targets of remission and LDA.

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REFERENCES
Molecular Signatures in Kidney Biopsies and Their Relationship to Clinical Activity

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Initiated to molecularly deconstruct lupus nephritis (LN), the Accelerating Medicines Partnership (AMP) is a public-private consortium involving the National Institutes of Health, pharmaceutical companies, and lupus investigators across fifteen clinical sites collecting urine, blood, skin biopsies, and kidney biopsies from patients with LN.

Almost 500 lupus patients have been enrolled in the AMP and their phenotypic data and specimens have been collected and applied to various technologies to provide insights into disease pathogenesis with the aim of facilitating more personalized medicine. Through several phases of AMP (technical preparation, pilot enrollment, and large-scale enrollment), 475 patients undergoing a clinically indicated percutaneous kidney biopsy consented to provide tissue for research. Overall, the rate of serious adverse events was 3.8%, consistent with that reported for standard procedures, supporting the safety of the procedure.1 The cohort is largely female and minority dominant. For nearly two thirds of the patients, this was a repeat biopsy. It was noted that the level of proteinuria did not predict histology class and most patients with a urine protein/creatinine ratio (UPCR) <1 had histology showing Class III, IV, V or mixed LN with accompanying activity and chronicity, despite an inactive sediment or normal serologies.2 These AMP data reinforced the consideration of renal biopsy at thresholds UPCR <1. For patients with UPCR >1, overall complete response rates were only 25%. Lower chronicity, but not activity, associated with complete response with proliferative histology being more responsive than membranous.

The earlier phases of AMP have yielded informative results based on single cell RNA sequencing. In brief, 21 subsets of leukocytes in LN were identified including multiple populations of myeloid cells, T cells, natural killer cells, and B cells.3 Cells expressed both pro-inflammatory and inflammation-resolving responses. Local activation of B cells correlated with an age-associated B-cell signature. Progressive stages of monocyte differentiation were evident. The majority of cells expressed a Type I interferon (IFN) response. Two chemokine receptors, CXCR4 and CX3CR1, were broadly expressed, which implicates a potential central role in cell trafficking. Kidney epithelial cells and M2-like macrophages may be coordinating traffic of immune cells infiltrating the kidney. A high Type I IFN response signature and fibrotic signature in tubular cells were each associated with non-response to therapy.4 Analysis of tubular cells from patients with proliferative, membranous, and mixed LN indicated pathways relevant to inflammation and fibrosis, which offer insight into their histological differences. Complete transcriptomic analysis of a larger dataset from 156 patients is underway.

References