relationship between intra-renal complement activation and kidney histology in LN, and whether complement activation products (CAPs) can serve as biomarkers to guide complement-directed therapies. In this investigation, urine CAPs levels were measured, and associations with kidney injury were determined.

Methods A cohort of 149 patients had urine and blood collected at the time of kidney biopsy for suspected LN. The CAPs C5a, C5b-9, and factor Ba were measured in the urine by ELISA. Biopsies were examined by routine histology, and the NIH activity and chronicity indexes (AI,CI) were calculated by two nephropathologists. CAPs levels were correlated with clinical and histologic data using the spearman correlation r.

Results The results are summarized in the table 1. The highest levels of CAPs were found in patients with proliferative or proliferative plus membranous LN, with lower levels in pure class II and V. All three urine CAPs correlated with AI, but the strongest correlation was between C5b-9 and AI. Only Ba and C5a correlated with CI, but this correlation was, at best, modest. All CAPs correlated with proteinuria, while only Ba and C5a correlated with serum creatinine.

Conclusion Urine C5b-9 was the best measure of histologic activity in LN. Given the size of the C5b-9 complex, it is unlikely to be filtered, even by glomeruli with a damaged glomerular permeability barrier. Urine C5b-9 therefore only reflects intra-renal complement activity. C5a and Ba associated modestly with active lesions, as well as kidney damage, likely accounting for their association with serum creatinine. We suggest levels of urine C5b-9 could be used to follow the success of anti-complement therapies in mitigating intra- renal complement activation in LN.

1102 THE TRAJECTORY OF GLOMERULAR AND TUBULOINTERSTITIAL LESIONS AFTER TREATMENT OF LUPUS NEPHRITIS

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Background Proliferative lupus nephritis (LN) is characterized histologically by glomerular and tubulointerstitial (TI) inflammation that presumably must resolve with treatment to achieve remission. Here we sought to document the trajectory of lesion resolution using serial kidney biopsies during LN treatment.

Methods A cohort of proliferative LN patients was prospectively followed during treatment with standard LN therapy. Patients had a diagnostic kidney biopsy (Bx1), a biopsy generally within the first year of treatment (Bx2), and a biopsy after at least 3 years of total immunosuppression (Bx3). The NIH activity and chronicity indices (AI, CI) were calculated at each biopsy.

Results The cohort (n=110) was followed for a median (range) of 109 (34, 202) months. Patients were treated with either MMF or cyclophosphamide initially. Overall, the patients did very well. Only 2 patients developed ESKD by last follow-up and only 9 patients had CKD (eGFR <60 ml/min/1.73m2), but this was pre-existing in 4 patients. AI followed an exponential decline after starting treatment. At the time of Bx2 (an average 9.7 months after Bx1), the percent of biopsies positive for cellular crescents (CC), fibrinoid necrosis (FN), and neutrophil infiltration NEU) fell precipitously, while the decline of endocapillary hypercellularity (EH) and hyaline deposits (HD) was more gradual. At Bx3 (an average of 42.6 months after Bx1) fewer than 5% of biopsies had residual CC, FN, NEU, or interstitial inflammation, but 25% still had EH and HD. By immunofluorescence microscopy over 90% of Bx1 biopsies had IgG and complement components C3 and C1q. At Bx3 only 30-40% of biopsies continued to show IF for complement, but IgG was still present in 66% of biopsies. The CI increased after Bx1. The rate of increase of all CI components was greatest from Bx1 to Bx2, slowed between Bx2 and Bx3, and actually declined for fibrous crescents.

Conclusion These data show that the most inflammatory lesions found in proliferative LN are rapidly responsive to immunosuppression, but EH and HD are more resistant. Complement deposition resolves quickly, but IgG is present in glomeruli for a long time. Despite rapid improvement in active inflammation, kidneys sustain chronic damage early in the disease course.

1103 LUPUS CLINICAL FLARES IN PATIENTS WITH GUT PATHOBIONT BLOOMS SHARE A NOVEL PERIPHERAL BLOOD TRANSCRIPTOMIC IMMUNE ACTIVATION PROFILE

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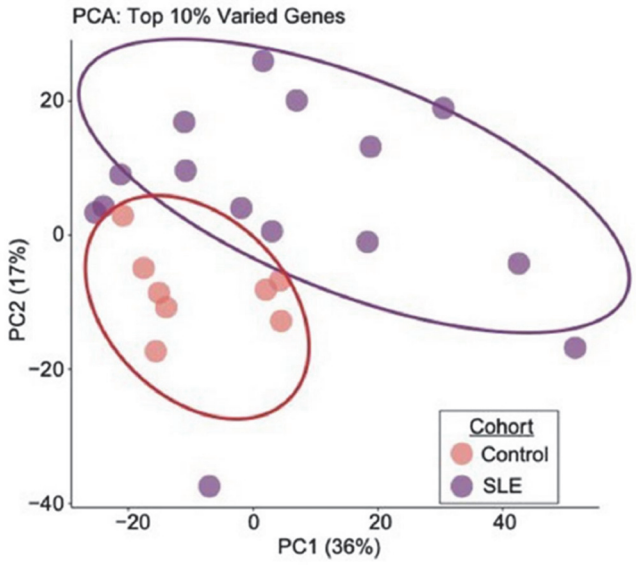
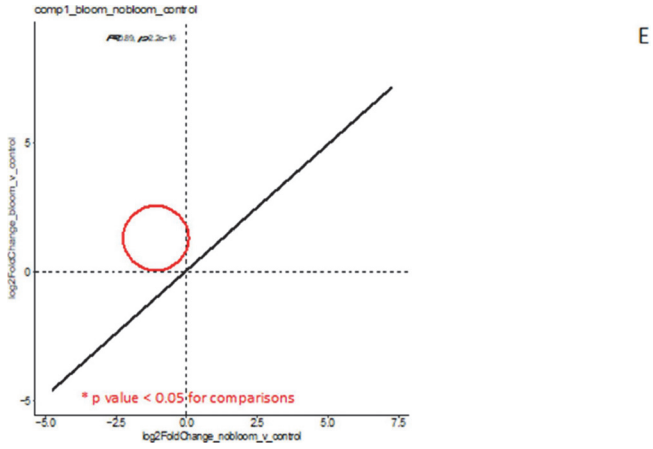
Background SLE is an inflammatory condition associated with hyperactivation of the immune system, with mounting evidence that imbalances in the gut microbiota communities are common. These imbalances can range from subtle patterns of dysbiosis to blooms in abundance of individual species that are concordant with clinical disease flares. Based on preliminary longitudinal surveys, almost half of Lupus nephritis (LN) flares were concurrent with transient expansions of a pathobiont, *Ruminococcus (blautia) gnavus*. As the transcriptomic patterns in the cells in our bloodstream can reflect disease activity, we sought to investigate gene expression patterns in groups of lupus patients, with comparisons to healthy controls (HC).

Methods From a well-characterized cohort, exploratory studies were performed on a selected group of 15 active female SLE patients, based in part on SLEDAI scores $\geq$ 4. Patients were grouped as without a history of renal involvement (i.e., non-renal) (N=7) or with LN in flare with Urine Protein creatinine ratio >0.5. Based on 16S rRNA fecal microbiota analyses, LN were subsetted as without bloom of individual species (N=4), or with a bloom (> 20-fold increased from HC, 3-9% abundance) of *R. gnavus* (N=4). In comparisons with 8 female HC, bulk RNA-seq was completed and after standard QC and filtering, 24,319 genes passed a minimum threshold of 4 reads in >50% samples and were used in downstream analysis.

Results Unsupervised clustering based on gene expression demonstrated significant separation between SLE samples and HC (figure 1). While there was no clear distinction between non-renal and renal (i.e., LN) groups, there were striking differences in the group of active LN without detectable gut



Abstract 1103 Figure 1 Principal Component Analysis show differences in gene expression of 15 female SLE patients and 8 healthy female controls.



Abstract 1103 Figure 2 Differential gene representation in the two LN flare groups compared with controls. Here, we have identified the gene transcripts with altered response to LN in the *R. gnavus* bloom (red circle).

microbiome blooms vs. active LN with *R. gnavus* blooms (figure 2), with 173 upregulated and 13 downregulated genes based on differential expression analysis (padj < 0.05, log2fc > 1). Gene set enrichment analysis (GSEA) identified several significantly altered pathways in the LN flare with blooms compared to no blooms, in highlighting multiple platelet activation pathways in the LN *with* blooms. In contrast, the LN flares *without* blooms had significantly higher interferon alpha and interferon gamma signatures.

Conclusion Our findings document two major types of flares of LN, with one being mediated by higher PBMC IFN- type I and -gamma transcript levels, and a second without this signature that instead is dominated by several pathways for platelet activation that can be responsible for systemic thromboinflammation. This second distinct pathways of immune activation in PBMC of LN in flare was concurrent with gut blooms of *R. gnavus*, a pathobiont that induces increased gut permeability, systemic inflammation, bacterial translocation and autoantibody production, which has a well-established association with active Lupus Nephritis. These findings may indicate that in a major subset of patients, LN flares may arise from severe perturbations of intestinal communities associated with a leaky gut, Together, this highlights *R. gnavus* as a potential causative agent for Lupus flares, in which we hypothesize that gut leak of innate immune stimuli, such as TLR2 and TLR4, which activate platelets in immune hyperactivation pathways that underlie lupus autoimmune pathogenesis.

1104 EFFECTS OF BELIMUMAB (BEL) ON RENAL OUTCOMES IN PATIENTS (PTS) WITH RELAPSED AND NEWLY DIAGNOSED ACTIVE LUPUS NEPHRITIS (LN)

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Background Despite standard therapy (ST) for LN, only 20–40% of pts achieve Complete Renal Response (CRR) at 0.5–1 year and 20–25% relapse in 3–5 years. Achieving CRR is often more difficult in relapsed patients than in *de novo* patients. The aim of this study was to assess effects of BEL on renal outcomes in relapsed and newly diagnosed pts with LN.

Methods A post hoc analysis of the Phase 3, randomized, double-blind, 104-week BLISS-LN study (GSK BEL114054; NCT01639339) was performed. Pts with active LN received monthly intravenous (IV) BEL 10 mg/kg or placebo (PBO) + ST. Randomization was stratified by induction regimen: high dose corticosteroids (HDCS) + cyclophosphamide (CYC), followed by azathioprine + low-dose corticosteroids (LDCS), or HDCS + mycophenolate mofetil (MMF), followed by MMF + LDCS. We assessed Primary Efficacy Renal Response (PERR; uPCR ≤0.7; eGFR no more than 20% below pre-flare value or ≥60 ml/min/1.73m^2; no rescue therapy) and CRR (uPCR <0.5; eGFR no more than 10% below pre-flare value or ≥90 ml/min/1.73m^2; no rescue therapy) at Week 104 and time to renal-related event or death in relapsed vs newly diagnosed pts.

Results Of 446 pts included in this analysis, 150 had relapse of LN and 296 were newly diagnosed. Positive effects of BEL vs PBO on PERR and CRR were noted in both subgroups but were numerically greater in relapsed vs newly diagnosed pts (table 1). BEL-treated pts had a lower risk at any time of experiencing a renal-related event or death vs PBO in both subgroups (table 1).

Conclusions These data suggest BEL improved PERR and CRR rates more potently in relapsed pts, in which PERR and CRR were substantially less frequent compared with newly diagnosed LN.

Acknowledgement Abstract[1] reprinted from ASN Kidney Week, October 25–November 7, 2021.