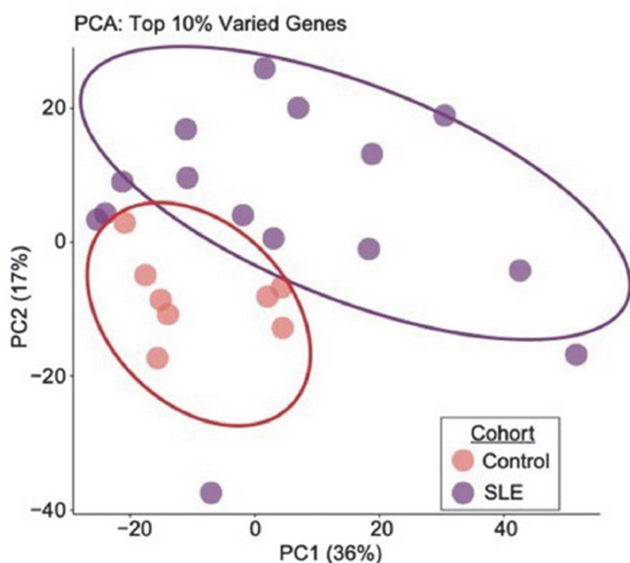
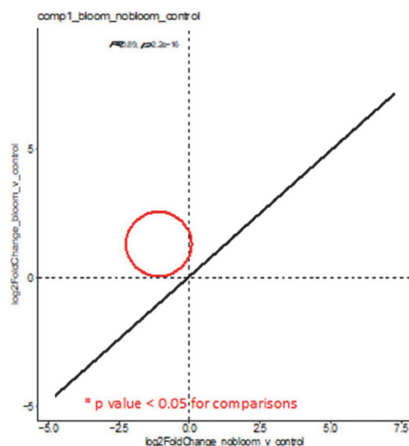


Abstract 1103 Figure 1 Principal Component Analysis show differences in gene expression of 15 female SLE patients and 8 healthy female controls.



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)

[1]Hans-Joachim Anders, [2]Brad H Rovin, [3]Ming-Hui Zhao, [4]Ana Malvar, [5]Keiju Hiromura, [6]Angela Jones- Leone, [6]Tania Gonzalez-Rivera, [7]Jennifer Gilbride, [6]Anuradha Madan, [8]Yulia Green, [6]David A Roth. *[1]Medizinische Klinik and Poliklinik IV, Klinikum der Universität München, Ludwig Maximilians University München, Munich, Germany; [2]The Ohio State University, Columbus, OH, USA; [3]Peking University First Hospital, Beijing, China; [4]Organizacion Medica de Investigacion, Buenos Aires, Argentina; [5]Department of Nephrology and Rheumatology, Gunma University Graduate School of Medicine, Maebashi, Japan; [6]GlaxoSmithKline, Collegeville, PA, USA; [7]GlaxoSmithKline, Stevenage, Hertfordshire, UK; [8]GlaxoSmithKline, Brentford, UK*

10.1136/lupus-2022-lupus21century.69

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.

Lupus Science & Medicine: first published as 10.1136/lupus-2022-lupus21century.69 on 14 December 2022. Downloaded from https://lupus.bmj.com on 6 November 2024 by guest. Protected by copyright.

Lupus Science & Medicine: first published as 10.1136/lupus-2022-lupus21century.69 on 14 December 2022. Downloaded from https://lupus.bmj.com on 6 November 2024 by guest. Protected by copyright.

Abstract 1104 Table 1 Effect of BEL 10 mg/kg IV on PERR and CRR at Week 104 and time to renal-related event or death in newly diagnosed and relapsed pts with LN

Table. Effect of BEL 10 mg/kg IV on PERR and CRR at Week 104 and time to renal-related event or death in newly diagnosed and relapsed pts with LN

	Relapsed		Newly diagnosed	
	PBO (n=75)	BEL 10 mg/kg IV (n=75)	PBO (n=148)	BEL 10 mg/kg IV (n=148)
PERR at Week 104, n (%)	17 (22.7)	27 (36.0)	55 (37.2)	69 (46.6)
OR (95% CI) vs PBO	2.31 (1.07, 5.01)		1.36 (0.85, 2.20)	
p-value	0.0331		0.2036	
CRR at Week 104, n (%)	8 (10.7)	17 (22.7)	36 (24.3)	50 (33.8)
OR (95% CI) vs PBO	3.11 (1.16, 8.31)		1.49 (0.88, 2.51)	
p-value	0.0237		0.1355	
Time to renal-related event or death*, n (%)	23 (30.7)	12 (16.0)	40 (27.0)	23 (15.5)
HR (95% CI) vs PBO	0.47 (0.23, 0.95)		0.55 (0.33, 0.93)	
p-value	0.0354		0.0242	

*Time to renal-related event or death is a composite endpoint defined as the first event occurring after Day 1 among the following: 1) death, 2) end-stage kidney disease, 3) doubling of serum creatinine, 4) renal worsening as evidenced by increased proteinuria and/or impaired renal function, or 5) renal disease-related treatment failure

OR, 95% CI and p-value are from a logistic regression model run within the subgroup level for the comparison between BEL and PBO with covariates of induction regimen (CYC vs MMF), race (Black African descent vs other), baseline uPCR, and baseline eGFR

HR, 95% CI and p-value from Cox proportional hazards model for the comparison between BEL and PBO adjusted for induction regimen (CYC vs MMF), race (Black African descent vs other), baseline uPCR, and baseline eGFR

CI, confidence interval; HR, hazard ratio; OR, odds ratio

REFERENCE

1. Hans-Joachim Anders, Brad Rovin, Ming-Hui Zhao, Ana Malvar, Keiju Hiromura, Angela R Jones- Leone, Tania Gonzalez Rivera, Jennifer Gilbride, Anu Madan, Yulia Green, David Roth. Effects of Belimumab (BEL) on Renal Outcomes in Patients With Relapsed and Newly Diagnosed Active Lupus Nephritis (LN). *J Am Soc Nephrol.* 2021;**32**:48.

Funding GSK.

Editorial assistance with encore abstract development was provided by Paragon, UK (funded by GSK).

Disclosures HJA has received consultancy fees from GSK, Novartis, AstraZeneca, Janssen, Kezar, Bayer, PreviPharma, Idorsia and Boehringer, and honoraria from GSK, Novartis, AstraZeneca, Janssen, Kezar, Bayer, PreviPharma, Idorsia, Boehringer, Lilly; is a Scientific Advisor/Membership for ERA-EDTA and an Associated editor at JASN and NDT. **BHR** has received consultancy fees from GSK. **MHZ** has received consultancy fees from GSK, AstraZeneca and Roche. **A Malvar** has received consultancy fees from GSK and Roche. **KH** has received consultancy fees from GSK. **AJL**, **TGR**, **JG**, **A Madan**, **YG** and **DAR** are employees of GSK and hold stocks and shares in the company.

1105 RESPONSE GENE TO COMPLEMENT-32 EXPRESSION IS UPREGULATED IN THE KIDNEY AND PROMOTES RENAL FIBROSIS IN LUPUS NEPHRITIS

Vinh Nguyen, Alex Tatomir, Cinthia Drachenberg, Horea Rus, Violeta Rus. *University of Maryland School of Medicine, Baltimore, MD, USA*

10.1136/lupus-2022-lupus21century.70

Background RGC (Response Gene to Complement)-32 is a cell cycle regulator widely expressed in normal tissues, multiple tumors and in a variety of cell lines. RGC-32 is localized in the cytoplasm and translocates to the nucleus upon upregulation by complement activation, growth factors and cytokines. Depending on the cell type, physiological or pathological conditions, RGC-32 can stimulate cell growth through increased p34CDC2 kinase activity and Akt phosphorylation or suppress it via arrest in mitotic progression. We have shown that RGC-32 is critical for murine and human Th17 cell differentiation. RGC-32 is induced by TGFβ in fibroblasts and human proximal tubular epithelial cells (PTEC) and mediates TGFβ dependent profibrotic pathways that contribute to renal fibrosis. RGC-32 expression has been described in tubules of normal human kidneys and its upregulation was reported in tubules from patients with IgA nephropathy. The expression patterns and function of RGC-32 in lupus nephritis (LN) have not yet been investigated.

Methods In situ expression and localization of RGC-32 was assessed by immunohistochemistry in kidney biopsies from 25 lupus patients with proliferative lupus nephritis and 11 patients with other nephropathies (IgA nephropathy, minimal change disease, ANCA-associated glomerulonephritis, nephrosclerosis, acute tubular necrosis). In vitro, the expression of RGC-32 in human PTEC cells was assessed by Flow cytometry, Western blot and RT-PCR in the presence or absence of cytokines with known nephritogenic potential such as IL-1, TNFα, IFNγ and TGFβ.

Results Consistent with the staining distribution reported in normal kidneys, RGC-32 immunostaining was predominant in proximal and distal tubules and was detected in a focal or diffuse pattern. Tubular mean staining intensity was significantly higher in SLE than in non-SLE specimens (2.0±0.23 vs 1.30 ±0.49; p=0.04) and was noted both in areas of normal appearing as well as damaged tubules. RGC-32 expression was also detected in glomeruli and in inflammatory cells in the interstitium of LN biopsies and colocalized with CD4+ T cells and CD68+ macrophages, respectively. Staining intensity was significantly higher in glomeruli and interstitium of LN