Abstract 503 Table 1 Steroid use provided by the standardized steroid regimen (SSR)

	INITIAL 4 WEEKS OF INDUCTION THERAPY	
	PO CS	**IV CS**
Patients ≥ 50 kg	Prednisone* 60 mg/day divided in up to 4 doses	Up to 3 doses (30 mg/kg; max 1 gram of methylprednisolone)
Patients < 50 kg	Prednisone 1.5 mg/kg/day	
Median – lowest PO CS dose at week 4**	40 mg/day - 30 mg/day	
WEEK 5 – 26 OF INDUCTION THERAPY (based on LN and ER trends since last visit)		
LN course *(assumption ER is stable)*	*Much worse*	Increase PO CS to 50-60mg/day; re-assess in 1-3 weeks; if response to increased PO CS is (a) *Satisfactory→ No IV CS; (b) non-satisfactory→ IV pulses + PO CS;* Possible change of immunosuppressive drug
	Mild – moderately worse	Increase PO CS by about 30% (if dose < 40 mg; max 60 mg)
	Active stable	Stable PO CS dose (if dose < 40 mg; else: slow decrease)
	Improved active or PRR[1]	Slow decrease of PO CS dose
	CRR[2]	More pronounced decrease of PO CS dose
ER course *(assumption LN is stable)*	*Much worse*	Increase PO CS dose; Re-assess in 1-3 weeks; if response to increased PO CS dose is (a) *Satisfactory→ No IV CS; (b) non-satisfactory→ IV pulses + PO CS dose;* Possible change of immunosuppressive drug
	Mild- moderately worse	Increase PO CS by 20% for doses < 40 mg; otherwise stable PO CS dose
	Active stable or improved active	Stable PO CS dose
	Inactive	Decrease PO CS dose
Median - Lowest PO CS dose possible at week 26	12.5 - 10 mg/day	
BEYOND 26 WEEKS POST KIDNEY BIOPSY - MAINTENANCE THERAPY		
LN course *(assumption ER is stable)*	Flare[3] after PRR/CRR	Prednisone ≥ 40 mg, irrespective of ER course Re-assess in 1-3 weeks; if response to increased PO CS is (a) *Satisfactory→ No IV CS; (b) non-satisfactory→ IV pulses + PO CS*
	Worse after PRR/CRR	Increase the PO CS dose FIRST
	PRR stable	Slow decrease of the SSR-dose
	Inactive/CRR or PRR improved	More pronounced decrease of the SSR dose
ER course *(assumption PRR parameters are stable)*	*Much worse*	Increase PO CS dose by 30-50% (max 60 mg) ; Re-assess in 1-3 weeks; if response to increased PO CS dose is (a) *Satisfactory→ No IV CS ; (b) non-satisfactory→ IV pulses + PO CS;* Possible change of immunosuppressive drug
	Mild- moderately worse	Increase PO CS dose by 25% for doses < 40 mg; otherwise stable PO CS dose
	Stable/Improved/Inactive	Decrease of the PO CS dose

** For patients ≥ 50 kg; * or corticosteroid equivalent dose.
[1]Partial renal remission (PRR): >50% improvement of ≥2 LN-RVs PLUS remaining LN-RV is NOT worse.
[2]Complete renal remission (CRR): All LN-RVs are NORMAL.
[3]LN flare defined by at least 1 of the LN-RV changes being persistently present on ≥2 subsequent time points ≥1week apart. LN-RV changes are defined as (a) newly abnormal GFR, (b) abnormal GFR that decreased by >10%, (c) persistent increase of UPCR to ≥0.5, after CRR, (d) persistent doubling of UPCR with values ≥1.0, after PRR, or (e) newly active or worsening glomerular hematuria.

Conclusions SSR for the treatment of cSLE complicated by LN has been developed which simulates PO/IV CS use among treating physicians. The proposed SSR may be useful for clinical care and to regulate background CS use during clinical trials of new medication for cSLE.

Acknowledgments Presented on behalf of the LaUNCH Project Investigator and supported by PORTICO (P30AR076316).

504 SPECIFIC *IN SITU* INFLAMMATORY ARCHITECTURES PREDICT PROGRESSION TO RENAL FAILURE IN HUMAN LUPUS NEPHRITIS

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10.1136/lupus-2021-lupus21century.22

Background In human lupus nephritis (LN), tubulointerstitial inflammation (TII) on biopsy predicts refractory disease and progression to end stage renal disease (ESRD). However, while approximately half of patients with moderate or severe TII develop ESRD, half do not. Therefore, we hypothesized that TII is heterogeneous with distinct inflammatory states each associated with different renal outcomes.

Methods We interrogated renal biopsies from LN longitudinal (55 patients) and cross-sectional cohorts using both conventional and highly-multiplex (24 analytes) confocal microscopy. To accurately segment cells across whole biopsies, and to understand their spatial relationships, we trained and implemented a suite of computer vision tools, including multiple parallel Mask-R convolutional neural networks. This evolution of our previous analytic pipeline, Cell Distance Mapping (CDM)(*Nat Immunol*, 2019, 20:503), we refer to as CDM version 4.

Results Across biopsies, B cell densities were strongly associated with protection from ESRD ($p=2x10^{-8}$, Mann-Whitney). In contrast, CD4- T cell population densities, which included CD8, gd and double negative (CD4-CD8-, DN) T cells, predicted progression to ESRD ($p=5.7x10^{-16}$). Breath first search and other analyses revealed inflammation was

organized into different discrete niches each with unique characteristics including enrichment for specific cell populations. B cell were often organized into large clusters with CD4 T cells including T follicular helper-like cells. In contrast, the CD4- T cell populations formed small dispersed clusters which, on a per patient basis, predicted progression to ESRD (p=0.004).

Conclusions These data reveal that in LN, specific *in situ* inflammatory states are associated with the failure of conventional therapy and progression to ESRD.

Acknowledgments These studies were funded by the NIH Autoimmunity Centers of Excellence and Lupus Research Alliance.

505 PARENCHYMAL INFγ RESPONSE REGULATES MURINE LUPUS NEPHRITIS

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10.1136/lupus-2021-lupus21century.23

Background Lupus nephritis is the most common life-threatening end-organ complication of SLE. Interstitial infiltrates, specifically T cells, are major predictors of disease outcomes. We recently determined that kidney-infiltrating T cells (KITs) are suppressed after kidney infiltration and exhibit an exhausted phenotype. Notably, the kidneys of nephritic lupus-prone (MRL.*Fas*^{lpr}) mice upregulate PD-L1, which we hypothesize is one mechanism inducing KIT suppression. IFNγ is the major inducer of PD-L1 and given the known role of IFNγ in lupus nephritis, we postulated that IFNγ induces a protective program in the kidneys of lupus-prone mice, in direct contrast to the proinflammatory role of IFNγ in the hematopoietic compartment.

Methods MRL. *Fas*^{lpr} mice develop autoantibodies, proteinuria, dermatitis, and glomerulonephritis. Others have previously shown that global IFNγ receptor deficiency (IFNγR$^{-/-}$) ameliorates disease in this mouse model. To determine if IFNγ signaling on parenchymal cells regulates disease, we generated bone marrow chimeras by transferring congenically labeled WT immune cells into either wild-type (WT) or IFNγR$^{-/-}$ MRL.*Fas*^{lpr} recipients. If our hypothesis is correct, then the IFNγR-/- recipients would have more severe disease than their WT counterparts. Chimerization occurred at 4-6 weeks of age and female and male mice were analyzed for disease pathology at 23 and 27 weeks post-chimerization respectively. Analysis included proteinuria, renal histology for both interstitial and glomerular disease, dermatitis, autoantibody production, and immune cell activation. Survival analysis was performed on female mice. Additional analysis focused specifically on T cell phenotypes.

Results IFNγR$^{-/-}$ MRL.*Fas*^{lpr} recipient mice exhibited more severe and rapid disease onset than WT recipient controls. While proteinuria was not different between the two groups, the IFNγR$^{-/-}$ recipients had more severe glomerulonephritis (p< 0.005) and interstitial disease (p< 0.001). Consistent with these findings, IFNγR$^{-/-}$ recipients had reduced survival (p< 0.05). As expected, IFNγR deficiency resulted in reduced PD-L1 expression. When examining infiltrates, KITs isolated from IFNγR$^{-/-}$ recipients exhibited increased expression of Tim3 and PD-1.

Conclusions These experiments suggest that parenchymal IFNγR signaling results in upregulation of protective mechanisms which reduce kidney disease and alter T cell phenotypes. This contrasts with global IFNγR$^{-/-}$ which ameliorated kidney disease. Overall, this finding argues that suppression of IFNγ, and possible other inflammatory mediators, may have differential effects on specific cell lineages and that global suppression of IFNγR may have both positive and negative effects on disease pathogenesis. This will need to be considered when devising targeted therapies.

Acknowledgments This work was supported by the Lupus Research Alliance (Novel Research Grant), NIAID (R01 AI137132), and J.T was supported by NIAMS 5K08AR075056.

506 BELIMUMAB (BEL) IMPROVES RENAL OUTCOMES IN ACTIVE LUPUS NEPHRITIS (LN): A PHASE 3 RANDOMIZED, PLACEBO (PBO)-CONTROLLED TRIAL

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10.1136/lupus-2021-lupus21century.24

Background BEL is approved for patients (pts) with systemic lupus erythematosus (SLE). We evaluated intravenous (IV) BEL in active LN.

Methods This 104-week trial (GSK Study BEL114054; NCT01639339) randomized adults with active LN (class III, IV, and/or V) 1:1 to monthly BEL 10 mg/kg IV or PBO, plus standard therapy (ST) with high-dose corticosteroids + either cyclophosphamide (CyC) or mycophenolate mofetil (MMF) for induction at the investigator's discretion. CyC was followed by azathioprine (AZA), and MMF by MMF maintenance. The primary endpoint was Primary Efficacy Renal Response (PERR = urine protein:creatinine ratio [uPCR] ≤0.7; estimated glomerular filtration rate [eGFR] no more than 20% below pre-flare value or ≥60 ml/min/1.73m^2; no rescue therapy) at Week 104. Other endpoints were Complete Renal Response (CRR = uPCR <0.5; eGFR no more than 10% below pre-flare value or ≥90 ml/min/1.73 m^2; no rescue therapy) at Week 104; time to renal event (end-stage kidney disease, doubling of serum creatinine, increased proteinuria and/or impaired renal function, renal disease-related treatment failure) or death. Endpoints were analyzed by ST regimen.

Results 224 pts were randomized to each arm. At Week 104, there were significantly more PERR and CRR responders on BEL vs PBO: (43.0% vs 32.3%, OR [95% CI] 1.6 [1.0, 2.3]; p=0.03) and (30.0% vs 19.7%, OR [95% CI] 1.7 [1.1, 2.7]; p=0.02), respectively. Risk of renal event or death was lower in BEL pts relative to PBO (HR [95% CI] 0.5 [0.3, 0.8]; p<0.01). Week 104 PERR response rates in pts on CyC/AZA were 33.9% with BEL and 27.1% with PBO, and 46.3% with BEL vs 34.1% with PBO in those on MMF. BEL reduced risk of renal event or death on background of CYC/AZA (HR [95% CI] 0.5 [0.2, 1.0]) and MMF (HR [95% CI] 0.5 [0.3,