Clinical Outcomes in Lupus Nephritis by Renal Response Status: A Retrospective Analysis of the Hopkins Lupus Cohort

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*At the time of the study

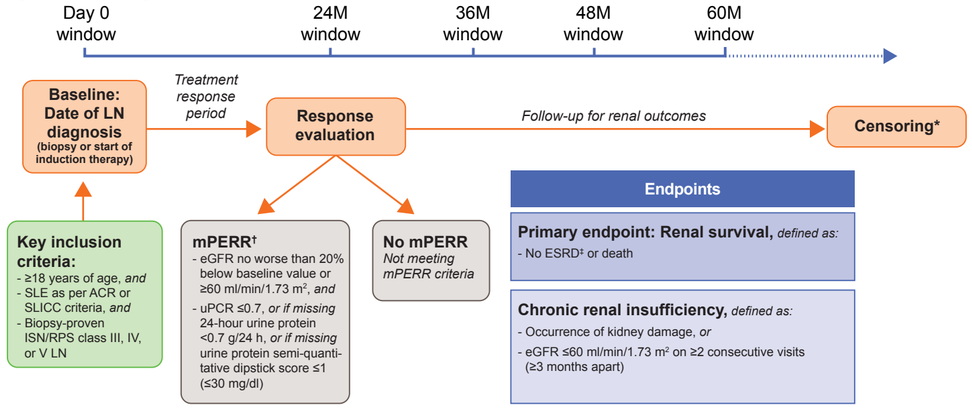
Introduction

- Lupus nephritis (LN) is a severe manifestation of systemic lupus erythematosus (SLE)[1]
- Approximately 22% of patients with LN develop end-stage renal disease (ESRD) within 15 years after diagnosis[2]
- Renal remission is a frequently assessed outcome in LN clinical trials; however, the definition of this endpoint varies across studies
- A previous study reported that the original primary endpoint of the Phase 3 study Efficacy and Safety of Belimumab in Patients with Active Lupus Nephritis (BLISS-LN; GlaxoSmithKline [GSK] study BEL114054; NCT01639339), renal response (complete/partial/none) at 24 months (24M) post LN diagnosis, was suitable to predict long-term renal outcomes[3]
- Based on emerging evidence on predictors of long-term outcomes in LN, the BLISS-LN primary endpoint was updated to the primary efficacy renal response (PERR) binary outcome (response/no response)

Objective

This study compared long-term renal survival and chronic renal insufficiency–free survival of patients who achieved mPERR at 24M after biopsy and those who did not

Figure 1: Study design



*Censoring occurred due to outcome event, loss to follow-up, or end of study dataset (December 2013); †As this was a real-world study, the BLISS-LN mandatory steroid tapering criteria were not included; ‡ESRD was captured prospectively during routine visits and defined as "clinical assessment of ESRD regardless of dialysis or transplant". ACR, American College of Rheumatology; ISN, International Society of Nephrology; RPS, Renal Pathology Society; SLICC, Systemic Lupus International Collaborating Clinics criteria; uPCR, urinary protein:creatinine ratio.

Methods

Study design

- This retrospective analysis (GSK study 213039) used health record data from eligible patients enrolled in the Hopkins Lupus Cohort, a prospective, longitudinal study of patients with SLE[4]
- PERR is a composite endpoint of estimated glomerular filtration rate (eGFR) and proteinuria thresholds. A modified PERR (mPERR) was used in this analysis to exclude urinary sediments (**Figure 1**)
- Renal outcomes were assessed during routine visits from 24M until censoring (**Figure 1**)
  - Due to the real-world setting, the timing of renal function assessments varied, and a ±3-month window for inclusion of laboratory data was defined around each interval date

Statistical analysis

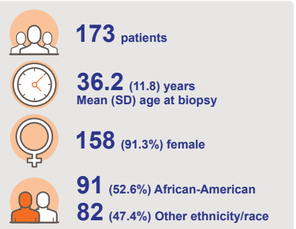
- Associations between mPERR status and renal survival (no ESRD or death) and chronic renal insufficiency–free survival were analyzed using Kaplan–Meier plots with log-rank tests
- Covariate-adjusted Cox proportional hazards models were used to evaluate the risk of renal death (ESRD or death), or developing chronic renal insufficiency during follow-up
  - The tested variables included: ISN class (III, IV or V), age, and SLICC Damage Index (SDI) score at baseline, as well as hydroxychloroquine use between baseline and 24M, hypertension, gender, and race/ethnicity, among others
  - Confounders were defined as remission variables that changed the hazard ratio (HR) by >10%

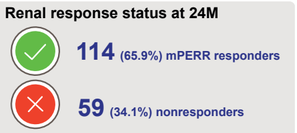
Results

Study population

- A total of 173 patients were included in the analysis (**Figure 2**)

Figure 2: Baseline* demographics and clinical characteristics





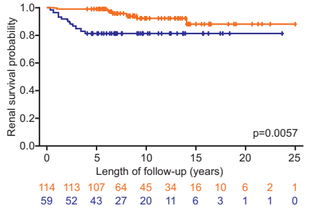
Clinical characteristics	
LN class, n (%)	
III	44 (25.4)
IV	50 (28.9)
V	39 (22.5)
Mixed	40 (23.1)
SDI, mean (SD)	2.2 (2.6)
Serum creatinine (mg/dl), mean (SD)	1 (0.6)
Urinary creatinine (mg/dl), mean (SD)	135.7 (110.2)
uPCR, mean (SD)	1.5 (1.8)
Hypertension†, n (%)	135 (78.0)
Diabetes, n (%)	27 (15.6)
History of MI, n (%)	4 (2.3)
Any hydroxychloroquine use from baseline to 24M, n (%)	120 (69.4)
Initiating induction therapy in 6 months before or after baseline, n (%)	
CYC	28 (16.2)
MMF	87 (50.3)
AZA	17 (9.8)
None	41 (23.7)
CYC or MMF or AZA	132 (76.3)

*Baseline=Biopsy date; †Defined as systolic blood pressure ≥140 or diastolic blood pressure ≥90 mmHg on 2 or more occasions *or* hypertension recorded as part of the SDI at any clinic visit. AZA, azathioprine; CYC, cyclophosphamide; MI, myocardial infarction; MMF, mycophenolate mofetil; SD, standard deviation.

Association between mPERR at 24M and renal survival

- Achieving mPERR at 24M was associated with an increased likelihood of long-term renal survival versus not achieving mPERR at 24M (**Figure 3**)

Figure 3: Likelihood of long-term renal survival (no ESRD or death) of mPERR responders (orange) and nonresponders (blue)



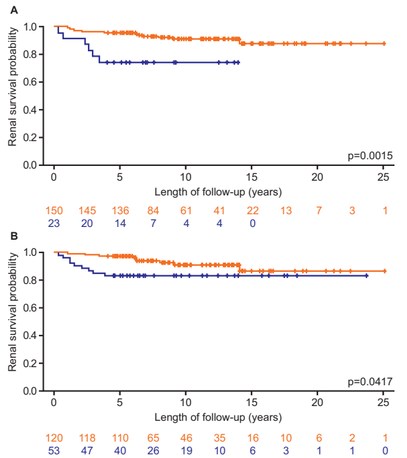
Analysis of renal survival by mPERR component

- Patients with eGFR criteria for mPERR at 24M post biopsy were significantly more likely to experience long-term renal survival than patients who did not meet eGFR criteria (p=0.0015; **Figure 4A**)
- Patients with low proteinuria levels at 24M were significantly more likely to experience long-term renal survival than patients with high proteinuria levels (p=0.0417; **Figure 4B**)

Association between mPERR status at 24M and chronic renal insufficiency

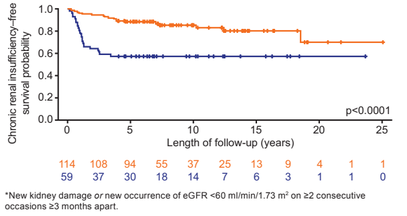
- Patients who achieved mPERR at 24M were significantly less likely to develop chronic renal insufficiency during the follow-up period than patients who did not achieve mPERR at 24M (p<0.0001; **Figure 5**)

Figure 4: Long-term renal survival* of responders (orange) and nonresponders (blue) by A) eGFR component†, and B) proteinuria component



*Due to the potential impact of censoring on the numbers of patients followed up over time, these results should be interpreted with caution; †Reduced length of follow-up for mPERR eGFR no response is due to no ESRD/mortality events occurring after this time point.

Figure 5: Chronic renal insufficiency–free* survival of mPERR responders (orange) and nonresponders (blue)



*New kidney damage *or* new occurrence of eGFR <60 ml/min/1.73 m² on ≥2 consecutive occasions ≥3 months apart.

Risk of renal death or chronic renal insufficiency by mPERR status at 24M

- Patients who did not achieve mPERR at 24M were at a higher risk of renal death (ESRD or death) and chronic renal insufficiency than mPERR responders (**Table 1**)

Table 1: Final multiple Cox proportional hazards models* for the association between mPERR category at 24M and renal death (ESRD/death) and chronic renal insufficiency

Study variable	Events (n)	Censored (n)	HR (95% CI)	p-value
Association between mPERR status and renal death (ESRD or death)				
mPERR at 24M	18	155	0.33 (0.13, 0.87)	0.0255
SDI	18	155	1.13 (0.99, 1.29)	0.0806
Hypertension	18	155	4.33 (0.57, 32.73)	0.1552
Association between mPERR status and chronic renal insufficiency				
mPERR at 24M	43	130	0.26 (0.14, 0.47)	<0.0001
Age at biopsy date	43	130	1.04 (1.02, 1.06)	0.0006
Hydroxychloroquine use from baseline to 24M	43	130	0.50 (0.27, 0.93)	0.0277

*Adjusted for covariates as described in the Methods. Variables that changed the renal remission variable HR by >10% were included in the final model. Where >2 potential confounders changed the HR by >10%, the confounders were ranked by degree of change and the top 2 were selected for entry into the model. CI, confidence interval.

Conclusions

- **Achieving mPERR at 24M post biopsy was associated with long-term renal survival and chronic renal insufficiency–free survival in patients with LN**
- **The composite endpoint of eGFR and proteinuria thresholds as defined in BLISS-LN was suitable to predict long-term renal outcomes**
- **Binary categories (ie, mPERR responders and nonresponders) for the mPERR endpoint were sufficient for predicting the likelihood of developing chronic renal insufficiency or renal death (ESRD or death)**
- **Multicenter studies are needed to validate the findings in a more diverse population**

References

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