Figure 1.

Conclusion: In patients with proliferative LN, proteinuric flares are a frequent event after induction treatment leads to CRR. Younger age, arterial hypertension, use of antihypertensive drugs and use of azathioprine as maintenance therapy were risk factors for LN proteinuric flare in this cohort.

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SAT0185

PREDICTORS OF POOR RENAL OUTCOME IN PATIENTS WITH PROLIFERATIVE LUPUS NEPHRITIS: A 36-MONTHS COHORT STUDY

M. Luis^{1,2}, A. R. Prata¹, H. Assunção¹, J. A. P. Da Silva^{1,2,3}, L. Inês^{1,4}.

¹Centro Hospitalar e Universitário de Coimbra, Rheumatology, Coimbra, Portugal; ²Faculty of Medicine, University of Coimbra, Coimbra, Portugal; ³Coimbra Institute for Clinical and Biomedical Research (ICBR), Coimbra, Portugal; ⁴School of Health Sciences, University of Beira Interior, Covilhã, Portugal

Background: The EULAR/ERA-EDTA recommendations for lupus nephritis (LN) state that renal response should be achieved within 12 months following induction therapy. However, there is an unmet need for early predictors of renal outcome in order to adjust the immunosuppression regimen and optimize the renal outcome.

Objectives: To identify predictors of poor renal outcome at baseline, 3 months and 6 months after starting induction therapy.

Methods: Retrospective cohort study over 36 months including patients with Systemic lupus erythematosus (SLE) fulfilling the ACR'97 and/or the SLICC'12 classification criteria and with biopsy-proven proliferative LN (class III/IV), enrolled in the CHUC Lupus Cohort from 1999 to 2018. Poor renal outcome was defined as longer time to complete renal response (CRR), characterized by proteinuria <0.5g/day and normal renal function, according to EULAR/ERA-EDTA criteria. Clinical-analytical characteristics at baseline, 3 months and 6 months after starting induction treatment were compared using survival analysis for time-to-CRR. Variables with $p < 0.25$ on univariate analysis using Log-Rank tests were further evaluated as predictors applying multivariate Cox proportional hazards regression models (Backward Stepwise method, Wald-based) with estimation of hazard ratios (HR) and 95% confidence intervals (95%CI).

Results: 56 patients were included (76.8% female, age at LN diagnosis 30.0 ± 13.2 years). Over the follow-up, 51 patients (91.1%) achieved CRR, within a median time of 6.0 months. In multivariate analysis, predictors of poor renal outcome were proteinuria $>2\text{g/day}$ at baseline (HR 1.98; 95%CI 1.04-3.77; $p=0.037$) and induction therapy with pulse cyclophosphamide (CYC), as compared to mycophenolate mofetil (MMF) (HR=2.05; 95%CI 1.07-3.94; $p=0.030$) (Figure 1). Diabetes mellitus (HR=6.0; 95%CI 1.24-29.07; $p=0.026$) and negative anti-RNP antibody (HR 3.17; 95%CI 1.27-7.93; $p=0.013$) at baseline predicted poor renal outcome at 3 months. At this timepoint, level of proteinuria and clearance rate were not predictive of renal response. At 6 months, no predictors of LN outcome were found for those patients that did not achieve CRR up to this timepoint. Use of glucocorticoid pulses and/or antihypertensive drugs did not predict LN outcome.

Figure 1.

Conclusion: In this SLE cohort, most patients with proliferative LN achieved CRR. Proteinuria above 2g/day at baseline and diabetes mellitus were predictors of poor renal outcome, while positive anti-RNP was protective. Induction treatment with CYC was associated with poorer outcome as compared with MMF. Given the retrospective non-randomized nature of this study, caution is needed when drawing conclusions regarding both treatments efficacy.

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SAT0186

DEVELOPING PREDICTORS OF GLOBAL BILAG TREATMENT RESPONSE IN PATIENTS WITH LUPUS NEPHRITIS: MORE LESSONS FROM THE ASPREVA LUPUS MANAGEMENT STUDY GROUP (ALMS) DATA

S. McDonald¹, S. Yiu², L. Su², C. Gordon³, N. Solomons⁴, I. N. Bruce^{1,5} on behalf of MASTERPLANS. ¹University of Manchester, NIHR Manchester BRC, Manchester, United Kingdom; ²University of Cambridge, MRC Biostatistics Unit, School of Clinical Medicine, Cambridge Institute of Public Health, Cambridge, United Kingdom; ³University of Birmingham, Institute of Inflammation and Ageing, Birmingham, United Kingdom; ⁴Aurinia Pharmaceuticals, Victoria, Canada; ⁵Manchester University NHS FT, Manchester Academic Health Science Centre, Manchester, United Kingdom

Background: Lupus Nephritis (LN) occurs in up to 60% of patients with SLE and is often associated with other organ involvement, morbidity and mortality. Treatment response and clinical improvement rates are limited with conventional therapy. Little is known about clinical predictors of response in SLE overall or in LN.

The ALMS induction trial compared mycophenolate mofetil (MMF) to IV cyclophosphamide (CYC) as induction for LN. MMF was deemed non-superior. The ALMS maintenance trial randomised responders to induction treatment at 6 months to MMF or Azathioprine, with MMF superior during follow-up.

Objectives: To identify predictors of overall clinical response at 6 and 12 months, in a cohort of SLE patients with LN.

Methods: Using the ALMS trial cohort, we analysed predictors of response in all the patients as a single cohort. 'Classic' BILAG scores were used to assess organ responses over time. Endpoints analysed were:

1) Improvement: defined as reduction in BILAG score to $\leq$ one BILAG B and no new BILAG organ domains involved, no increase in steroids from baseline and no increase in SLEDAI from baseline.

2) Major Clinical Response (MCR): defined as reduction in BILAG score to BILAG C in all domains, a reduction in steroid dose to $\leq 7.5\text{mg}$ daily and a SLEDAI score ≤ 4 . Potential predictors examined included baseline demographics, medication, disease activity (BILAG, SLEDAI), SLICC/ACR damage index (SDI) and serology. Univariate logistic regressions were used to provide odds ratios of predictors. Multivariate logistic regressions with LASSO and cross-validation in randomly split samples were utilised to build prediction models. Predictors were ranked by the percentage of times they were selected by LASSO.

Results: 370 patients enrolled in the ALMS induction trial. 227 patients were randomised at 6 months to maintenance. 313(84.59%) patients were female. 147(39.72%) patients were Caucasian. The mean age was 31.9 years.

236(63.78%) patients had a disease duration of LN of < 1 year. Baseline mean($\pm$ SD) SLEDAI score was 15.28 ($\pm$ 6.78) and mean($\pm$ SD) numerical BILAG score was 19.61($\pm$ 7.67). Improvement at 6 months was attained by 180 (48.65%). Predictors included older age (OR=1.03 [95% CI: 1.01,1.05] per year) and normal haemoglobin (OR=1.90 [95% CI: 1.19, 3.05] vs low hb). Activity (BILAG A or B) in haematological and mucocutaneous domains predicted less improvement (OR [95% CI] = 0.59 [95% CI: 0.38, 0.94] and 0.50 [95% CI: 0.31,0.82] respectively). Baseline damage (SDI >1) negatively predicted improvement (OR 0.54 [95% CI: 0.31,0.92]). Improvement at 12 months was achieved by 139 (37.57%). Low IgG predicted improvement (OR 4.66 [95% CI: 1.34,16.23]. Black US patients were less likely to improve (OR 0.29 [95% CI: 0.06,0.90] vs Asian patients). MCR was achieved by 14(3.79%) and 40(10.81%) at 6 and 12 months. We found regional and racial differences in 12-month MCR responses (Figure 1). Baseline normal C4 predicted a decreased likelihood of MCR (OR 0.37 [95% CI: 0.17,0.64] vs normal C4).

Figure 1. Univariate analysis of Improvement at 6 and 12 months and MCR at 12 months.

Results of multivariate logistic regression with LASSO were consistent with the univariate analyses.

Conclusion: A number of factors were related to improvement and MCR in conventionally treated LN patients. Those with damage and active non-renal disease were less likely to improve at 6 months. Baseline low C4 increased MCR likelihood at 12 months. These factors may help stratify patients based on likelihood of response and help select patients who may need alternative treatment strategies.

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SAT0187

DISCRIMINATION OF SYSTEMIC LUPUS (SLE) PATIENTS WITH CLINICAL RESPONSE TO OBEXELIMAB (XMAB#5871) BASED ON A PATTERN OF IMMUNOLOGIC MARKERS

J. T. Merrill^{1,2}, J. Guthridge¹, D. Zack³, P. Foster³, B. Burington³, L. Tran¹, M. Smith¹, J. A. James^{1,2}, ¹Oklahoma Medical Research Foundation, Arthritis & Clinical Immunology Program, Oklahoma City, United States of America; ²University of Oklahoma Health Sciences Center, Medicine, Oklahoma City, United States of America; ³Xencor, Monrovia, United States of America

Background: We recently reported Phase 2 SLE trial results of obexelimab, an FcγRIIb agonist (suppressor of B cell activation). Obexelimab did not meet the primary endpoint (% of patients without flare at Day 225) (p=0.183) but other endpoints such as time to flare (p=0.025) were met.

Objectives: 1. To assign SLE patients to phenotypic subsets based on patterns of gene expression in immune-related pathways.¹ 2. To explore the association of immune patterns and clinical response to obexelimab.

Methods: This analysis included 71 of the 104 participants in the obexelimab study, those who either completed the protocol or terminated for disease flare, if there were adequate blood samples (biomarker subset). At screening, patients were assigned to clusters based on 41 SLE co-expression signature modules from the Human Immune Phenotyping Consortium via unsupervised random forest and K-means clustering.² Other markers of SLE disease were also examined. The BOLD³ study design mandated withdrawal of background immunosuppressants, supporting less ambiguous pharmacodynamic analysis as the trial progressed.

Results: Immune pathway expression patterns of 7 patient clusters (Fig 1a) confirmed our prior characterization of 200 non-overlapping SLE patients.² The biomarker subset retained a trend of longer time to first flare in patients receiving obexelimab (n=38) vs placebo (n=33) (Fig1b, HR 0.61, p=0.11). A smaller set of only Clusters 3 and 6 demonstrated marked increased time to flare in the obexelimab group (n=13) compared to placebo (n=14) (Fig 1c, HR 0.22, p=0.025). Obexelimab had no effect on other clusters (Fig 1d). The responder clusters shared low expression of inflammation modules (p < 0.001) compared to other clusters and high expression of T Cell, immune response, cell cycle, mitochondrial modules (all p < 0.001) and B Cell modules (p=0.006). We therefore sorted patients by these specific features regardless of cluster assignment. Figure 2 shows significant impact of obexelimab on time to flare in 64 patients with B Cell pathway activation (HR 0.5, p=0.038), although less robust by itself than found in Clusters 3 and 6. In a group with high B or plasma cell modules but low inflammation (n=46), treatment effect increased (HR 0.35, p=0.019). Between Screening and Baseline, as brief steroids were given and background treatments withdrawn, expression of B Cell and Plasma Cell pathways increased. Both then decreased after treatment with obexelimab but not placebo (p< 0.0001 and p< 0.001 respectively), an effect not seen with other immune pathway modules.

Conclusion: Precision medicine for SLE has been hampered by heterogenous immune signals with variable expression. Clustering of patients by gene co-expression pathways enabled an efficient, hierarchical array that reduplicated results of a prior SLE cohort, suggesting these are not random phenotypes. Of these 7 reproducible SLE subsets, the combination of clusters 3 and 6 distinguished an obexelimab responder population of 27 out of 71 subjects (38%) with high expression of B and T Cell modules and cell activation pathways. Focus on the defining features shared by these clusters revealed specific factors associated with response, enabling inclusion of some patients from other clusters in an optimized responder population of 46/71 (65% of subjects). B Cell and Plasma Cell pathways demonstrated mechanism-related pharmacodynamic effects of obexelimab. Lack of responders with high expression of inflammation modules could implicate inhibitory factors to obexelimab within inflammatory pathways, potentially targetable by complementary treatments.

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Fig 1: Effects of Obexelimab Treatment on Time to Flare in SLE Patient Subsets Defined by Patterns of Gene Co-Expression Pathways