had nonsignificant results, possibly due to the small sample size, especially for mortality.

The multivariable models were adjusted for baseline covariates including demographic variables (age, sex, location of residence, neighborhood income quintile), indicator of having RA or SLE (not considered for individual RA and SLE patients cases), health resource utilization (hospital visits, physician and specialist visits including rheumatologist, nephrologist, and psychiatrist visits), medication usage (statins, other cardiovascular drugs, hormone replacement therapy, glucocorticoids, anticoagulant therapy, Cox-2 inhibitors, immunosuppressive drugs), comorbidities (hypertension, chronic obstructive pulmonary disease, angina), and the Romano adaptation of the Charlson comorbidity index for administrative data. Also, the time-varying variables of health resource utilization, medication usage, Charlson comorbidity index, and comorbidities were used to calculate weights in marginal structural model.

Conclusions SLE and RA patients' adherent to AM therapy had 53% and 30% lower risk of CVD mortality and incident CVD events, respectively, than partially adherent patients.

500 – Lupus nephritis

501 ANTI-LG3 ANTIBODIES CONTRIBUTE TO MICROVASCULAR LOSS AND FIBROSIS IN LUPUS NEPHRITIS

[1,2,3]Marie-Hélene Normand, [2,3,4]Shanshan Lan, [1,2,3]Sandrine Juillard, [2,3]Julie Turgeon, [2]Annie Karakeussian-Rimbaud, [2,3]Francis Migneault, Éric Boilard [3,5]Guillaume Bollée [2,42,3,4]Marie-Josée Hébert, [1,2,3]Mélanie Dieudé*. *[1]Département Microbiologie, Infectiologie et Immunologie, Faculté de Médecine, Université de Montréal; [2]Centre de Recherche du CHUM (CRCHUM); [3]Canadian Donation and Transplantation Research Program (CDTRP); [4]Université de Montréal; [5]Université Laval*

10.1136/lupus-2021-lupus21century.19

Background Lupus nephritis (LN) is a common and serious manifestation of systemic lupus erythematosus (SLE) and 30% of cases, affected patients progress to end stage renal disease (ESRD). Microvascular damage is an emerging contributing factor to LN renal dysfunction leading to end stage renal disease. We have shown that vascular injury derived apoptotic exosomes can trigger SLE autoantibodies as well as autoantibodies targeting perlecan/LG3 (anti- LG3). We have also unraveled biomarkers and effector roles of anti-LG3 in kidney vascular damage in both native and transplanted kidneys. We hypothesize that anti-LG3 responses contribute to microvascular damage of importance in LN development.

Methods Longitudinal bleeds were performed on SLE prone NZB/NZWF1 and control mice. Circulating Anti-LG3 IgG levels were measured by ELISA. 26 weeks old NZB/NZWF1 mice were infused with anti-LG3 or control IgG, every second day for 3 weeks. Kidneys were harvested at sacrifice for renal histology and immunohistochemistry analyses. PTC capillary loss was evaluated with MECA-32 staining and renal interstitial fibrosis aSMA and Collagen IV staining.

Results Elevated levels of anti-LG3 are found in SLE prone mice, compared to control mice. Importantly, NZB/NZWF1 mice passively transferred with anti-LG3 exhibited significantly increased interstitial inflammation, PTC capillary loss, and renal interstitial fibrosis in the absence of glomerular abnormalities (crescents and proliferation), compared to mice transferred with control IgG.

Conclusions These observations suggest that anti-LG3 antibodies are elevated in SLE and show a tropism specific for the interstitial microvasculature, contributing to microvascular loss and fibrosis. A better understanding of the impact of these novel biomarkers and effector will improve identification, prediction, and management of LN.

502 ENVIRONMENTAL ADAPTATION AND TISSUE INJURY IN LUPUS

Ping-Men Chen, Joseph Craft*. *Yale University*

10.1136/lupus-2021-lupus21century.20

Background Tissue injury with progressive damage is a major cause of morbidity and mortality in SLE. Yet, there is limited knowledge of the mechanistic pathways that contribute to tissue injury in lupus. We hypothesize that local environmental factors dictate effector function of tissue-infiltrating immune cells in target organs in SLE, to initiate and sustain damage, with therapeutic targeting of these maladaptive changes able to reverse damage. Our hypothesis is based upon the idea that local microenvironment naturally responds to stress or insult, such as mediated by glomerular immune complex deposition or environmental damage to the skin, with changes in the local microenvironment affecting immune-cell phenotype and function.

Methods and Results To identify tissue-adaptive pathways mediated by the local microenvironment that initiate and sustain organ injury, we dissected tissue-infiltrating T cells in the lupus kidney, building upon the longstanding observation that T effector cells are necessary for the local inflammatory response. For example, tissues become hypoxic as a common denominator as an appropriately physiologic response occurring at sites of pathogen replication or in tumors to ensure lymphocyte survival and effector function. The kidney, naturally hypoxic at the corticomedullary junction and in the medulla, becomes even more hypoxic during inflammation. We demonstrated that upon renal infiltration, T cells adapt to the hypoxic environment, without exhaustion, to ensure their survival and effector capability, with remodeling of metabolic and epigenetic pathways with tissue damage driven by a hypoxia-dependent, transcriptionally regulated inflammatory gene program. Tissue hypoxia was initiated by autoantibody-dependent glomerular immune complex formation, with subsequent renal entry of T cells that environmentally adapt with tissue-damaging effector function of a type 1 (Th1 or Tc1) phenotype. Survival was sustained by genetic and metabolic reprogramming of $CD4^+$ and $CD8^+$ T cells, including alteration in cell death and energy utilization pathways. Selective genetic, or more practically, pharmacologic blockade of tissue-adaptive pathways dampened activated T-cell function, reversing tissue hypoxia and alleviating established damage. The same pathways are operative in human lupus nephritis.

Conclusions We demonstrate that upon infiltration into the kidney, T cells adapt to the local environment to ensure their survival and effector capability, with remodeling of metabolic pathways. Although beneficial to the host upon local pathogen invasion, such changes in lupus are maladaptive, leading to tissue damage. Understanding phenotypic changes in renal-infiltrating immune cells can lead to therapeutic targeting with disease amelioration.

Lupus Sci Med: first published as 10.1136/lupus-2021-lupus21century.20 on 4 November 2021. Downloaded from http://lupus.bmj.com/ on February 26, 2024 by guest. Protected by copyright.

Acknowledgements Supported by a Pilot & Feasibility Grant from the George M. O'Brien Center for Kidney Research at Yale (NIH P30 DK079310, J.C.), grants from the NIH R37 AR40072 (J.C.), R01 AR074545 (J.C.), and R21 AI142145 (J. C), NIH U19 AI082724 (M.R.C), and AbbVie (J.C.). P.M.C. was the recipient of government scholarship for graduate study from the Ministry of Education, Taiwan, and Gershon Fellowship from the Department of Immunobiology, Yale University.

503 DEVELOPING A STANDARDIZED STEROID DOSING REGIMEN IN PEDIATRIC PROLIFERATIVE LUPUS NEPHRITIS

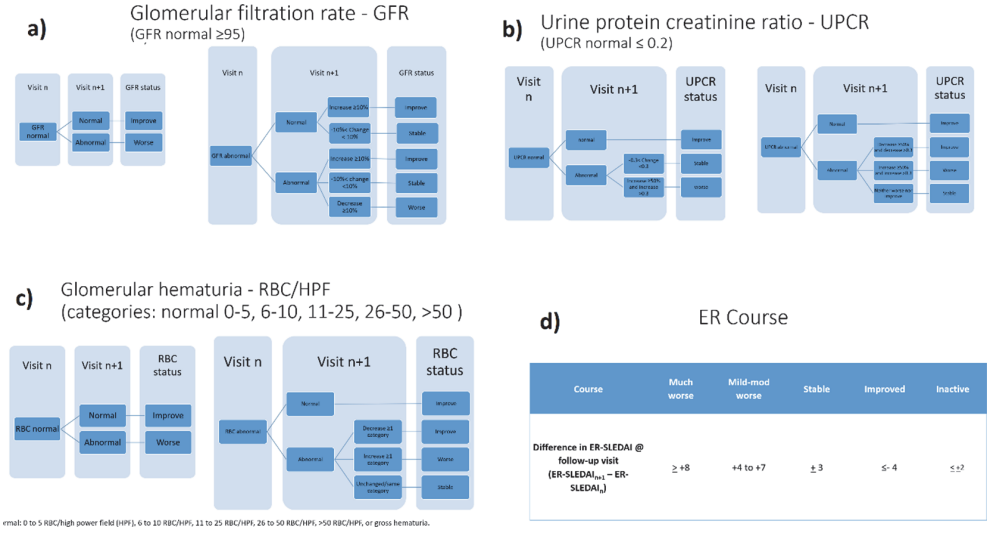
[1]Hermine I Brunner*, [2]K Rouster-Stevens, [3]Marisa S Klein-Gitelman, [4]Karen Onel, [5]Beatrice Goilav, [6]Natasha Ruth, [1]Tingting Qiu, [1]Najla Aljaberi, [7]Jianghong Deng, [8]Benjamin L Laskin, [9]Anna Carmela P Sagcal-Gironella, [10]Stacy P Ardoin, [11]Deborah M Levy, [9]Scott E Wenderfer, [1]Bin Huang. *[1]Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA; [2]Emory University, Children's Healthcare of Atlanta, Atlanta, Georgia, USA; [3]Northwestern University Feinberg School of Medicine, Ann and Robert H Lurie Children's Hospital of Chicago, Chicago, IL, USA; [4]Division of Pediatric Rheumatology, Hospital for Special Surgery, New York, NY, USA; [5]The Children's Hospital at Montefiore, Albert Einstein College of Medicine, Bronx, NY, USA; [6]Medical University of South Carolina, Charleston, South Carolina, USA; [7]Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China; [8]Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [9]Department of Pediatrics, Baylor College of Medicine, Houston, Texas, USA; [10]Nationwide Children's Hospital, Columbus, Ohio, USA; [11]The Hospital for Sick Children and The University of Toronto, Toronto, Ontario, Canada*

10.1136/lupus-2021-lupus21century.21

Background Corticosteroids (CS) remain the mainstay of therapy for childhood-onset systemic lupus erythematosus (cSLE) although there are no widely accepted dosing strategies of oral (PO CS) or intravenous CS (IV CS). We aimed to (1) develop a standardized CS dosing regimen (SSR) and (2) achieve consensus for this SSR among pediatric rheumatology and nephrology providers treating cSLE complicated by lupus nephritis (LN).

Methods Consensus formation techniques were used. A Delphi questionnaire pertaining to CS use in cSLE was completed to inform formats of the Patient Profiles (PP, Step 1). Using data from 147 children with proliferative LN at 8 major cSLE treatment sites in North America PP were generated providing information about the course of LN and extra-renal cSLE (ER) at 2 subsequent visits (Step 2). PP were sent to 142 physicians (PP-raters) experienced in cSLE to adjudicate the course of ER and LN and propose the PO/IV CS dosages (Step 3). Using data from PP for which consensus was achieved, the SSR was developed (Step 4) and refined based on responses from another questionnaire and a focus group of experienced physicians (Step 5). The SSR was tested using a second type of PP that described ER and LN courses for 6 months from the time of biopsy (Step 6). Consensus was defined as agreement of the majority of PP-raters (Step 3, Step 6).

Results For Step 1 and Step 3, 103 physicians answered Delphi questions and filled 353 PP (response rate: 73%). Step 6 activities were completed by 18 physicians (13.4 years of average experience) who were asked to review 33 PP each. This resulted in 564 completed PP ratings, of which 437 (77.5%) and 460 (81.6%) ratings yielded consensus on POSSR-and IV SSR dosing, respectively. PO CS and/or IV CS dosages as per the SSR (SSR-dose) depend on patient weight, the course of ER activity measured by the ER-SLE-DAI score (figure 1d), and the course of LN described by changes/status of 3 *LN response variables (LN-RVs*, figure 1a-c). The SSR mimics dosing customs agreed upon by the PP-raters. Table 1 summarizes the SSR with focus on 2 ER/LN settings (1:stable ER/various LN courses; 2:stable LN/various ER courses), with several permutation of the course of ER (much worse, mild-moderately worse, active stable/improved, inactive) and LN (flare, mild-moderately worse, active stable/improved/partial renal remission (PRR), complete renal remission (CRR)). Use of dosages of PO CS $\geq$ 40 mg are governed by the course of LN except in major ER flares with potential organ damage. The SSR adjusts PO CS dosages in at least monthly intervals. IV CS are used for worsening of ER or LN courses that fail to respond to increased oral CS of $\geq$ 40 mg up to 4 weeks. Small decreases of PO CS occur even with stable ER or stable LN activity. Achieving CRR leads to more pronounced reduction of PO CS (table 1). Beyond 6 months post kidney biopsy (maintenance therapy), the PO/IV CS dosage is informed by LN status (PRR, CRR), the course of LN and ER activity (table 1).



Abstract 503 Figure 1

Lupus Sci Med: first published as 10.1136/lupus-2021-lupus21century.20 on 4 November 2021. Downloaded from http://lupus.bmj.com/ on February 26, 2024 by guest. Protected by copyright.