**SUPPLEMENTARY MATERIAL**

**Study population**

Four centers participated in this consortium study: University College London (UCL), Leiden University Medical Center (LUMC), Freiburg University Medical Center and the Charité University Medical Center in Berlin. Severe SLE was defined as new, worse or persistent SLE-activity in major organs, or an SLE disease activity index (SLEDAI) score of 12 or more points, or a BILAG A score and/or two B scores. Refractory disease was defined as the failure to respond to, or two documented adverse events to the standard immunosuppressive therapies (mycophenolate mofetil (MMF) or cyclophosphamide (CYC), unless contraindicated). Therapeutic decisions were at the discretion of the treating physician (rheumatologist/nephrologist) at each center. Because of the different treatment regimens with distinct pharmacokinetics, the post-treatment assessment varied per treatment protocol: after a median of 30 [IQR:25-33] weeks in the RTX cohort, after 24 [24-24] weeks in RTX+BLM cohort and after 6 [4-7] weeks in the BTZ-treated cohort. For BTZ patients an additional follow-up sample was available after a median of 12 [9-14] weeks. SLE disease activity assessments were recorded by BILAG scores in London and SLEDAI-2K was used in the other centers, whereas a good correlation between these systems has been demonstrated(1). CD19+ B-cell values were missing for 5 BTZ-treated SLE patients.

**Autoantibody measurements**

96-well plate microtiter ELISA plates (Nunc Maxisorb, Thermo Fisher, Waltham, USA) were coated with 2,5 µg/ml ultrapure calf thymus DNA solution (Thermofisher, Waltham, USA),2 µg/ml protein-stripped recombinant human mononucleosomes (EpiCypher, the Netherlands)or 10 µg/ml purified mixture of isolated calf thymus histones (Roche, Basel, Switserland) overnight at room temperature (RT) in 100uL. The purity of the calf thymus DNA solution, recombinant mono-nucleosomes and calf thymus histones were confirmed by an agarose and polyacrylamide gel (data not shown). Histones mixture contained H1, H2A, H2B, H3 and H4 but no DNA. The mononucleosomes contained H2A, H2B, H3 and H4 and a 147 base pairs DNA strand. Calf thymus DNA and recombinant mononucleosomes were both diluted in reacti-bindTM DNA coating solution (Thermofisher, Waltham, USA), because DNA has a low binding affinity for unmodified plastic surfaces34 and calf thymus histones were dissolved in sodium carbonate buffer. Bovine serum albumin (BSA) was avoided because anti-BSA antibodies have been reported in some SLE patients36. After coating, plates were washed with PBS/0.05% Tween 20 and blocked with 100 µl/well PBS/Casein 2% (Sigma, Saint-Louis, USA) 1 hour at 37oC. Wells were washed and sera were diluted (optimal dilution was determined by titration per ELISA) in PBS/0.05% Tween 20/Casein 2% (Tween 20, Sigma, Saint-Louis, USA) and incubated for 1 hour at 37oC. Autoantibodies in sera were detected with 1:12000 diluted polyclonal rabbit-α-human-IgG/HRP secondary antibody (Dako, Jena, Germany, stock: 1.3 g/L). 100 µl/well 3,3',5,5'-Tetramethylbenzidine (TMB) (Sigma, Saint-Louis, USA) was used as a substrate for the revelation of HRP for approximately 20 – 30 minutes in the dark. The color reaction was stopped with 100 µl/well sulfuric acid, H2SO4, TMB-stop solution (Merck, Darmstadt, Germany). The optical density (OD) was measured at 450 nm wavelength (Bio-Rad, Hercules, USA). Serum of a SLE patient with high titers was chosen as standard for each ELISA and was given an Arbitrary unit/ml (AU/ml). Negative cut-off values were determined per ELISA at the mean ±2SD AU/ml of fifteen normal human serum (NHS), which were 21.7 AU/ml for the anti-dsDNA, 28 AU/ml for the anti-histone and 7 AU/ml for the anti-nucleosome in-house ELISAs. Anti-C1q IgG autoantibodies were measured with the commercial QUANTA lite assay according to manufactures’ instructions (INOVA diagnostics, San Diego, USA). To detect anti-TT IgG with an in-house ELISA, Tetanus Toxoid (NIBSC, South Mimms, UK) was coated at a concentration of 1.5LF/ml. Blocking and washing were similar as described above except that the plates are stained with 1:5000 goat anti-human IgG HRP (DAKO, Jena, Germany) and ABTS containing 2 µl hydrogen peroxide 30% (Sigma-Aldrich, Darmstadt, Germany) was used as a substrate.

**Anti-Tetanus Toxoid IgG and anti-dsDNA IgG avidity measurement**

Avidity of anti-dsDNA IgG was measured by an elution ELISA modified from a previous publication(2, 3). Coating and blocking of the ELISAs were performed as described previously. After sera were incubated at optimal dilution the plates were washed 3 times with PBS-Tween and the wells were incubated 15 minutes at room temperature with a variable molarity (range 0.0625-10M) of the chaotropic agent sodium thiocyanate (NaSCN, Sigma). After vigorous washing (5 times) with PBS-tween, the conjugate and colour reactions were performed according to the corresponding ELISA as described in supplementary materials 1. Low avidity antibodies were arbitrarily defined as antibodies that were eluted from the coated antigen with less than 0.25M NaSCN. Medium avidity antibodies were defined as antibodies that were eluted with 0.25 to <1M NaSCN. High avidity antibodies were defined as antibodies that were eluted with ≥1M NaSCN. An example of avidity curves for anti-dsDNA and anti-tetanus toxoid (TT) IgG are displayed in supplemental figure 1A and the distribution and analysis of low, medium and high avidity antibodies in supplemental figure 1B.

**Preparation of neutrophils and quantification of NETs**

Neutrophils were isolated as described before(4). Briefly, ficoll-amidotrizoaat (LUMC, Netherlands) was used to isolate neutrophils from whole blood of HCs followed by erythrocyte lysis with sterilized water at 4⁰C. PKH-labelled neutrophils were plated 37.500 per well in a 96-well plate (Falcon, USA), in 2% FCS RPMI medium (LifeTechnologies, Netherlands). Unstimulated neutrophils and neutrophils stimulated with normal human serum (NHS) were taken along as controls. Briefly, 12 z-stacked images of 25 predefined high power fields (HPFs) at a 20x magnification were automatically captured to image a total of 11.1% of the well. For each image, PKH26 (Cy3) and Sytox green (Alexa488) were visualized with the same exposure time applied to all images within the same experiment. Acquired images were semi-automatically analyzed by ImageJ image analysis software (NIH, Bethesda, USA). NET formation was quantified as the cumulative area of extracellular DNA (Sytoxgreen) over 12 z-stacks and corrected by the number of neutrophils, as reflected by the PKH area by ImageJ software (NIH, USA). Median value of each sera tested in triplo was presented.

1. Romero-Diaz J, Isenberg D, Ramsey-Goldman R. Measures of adult systemic lupus erythematosus: updated version of British Isles Lupus Assessment Group (BILAG 2004), European Consensus Lupus Activity Measurements (ECLAM), Systemic Lupus Activity Measure, Revised (SLAM-R), Systemic Lupus Activity Questionnaire for Population Studies (SLAQ), Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), and Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI). Arthritis care & research. 2011;63 Suppl 11:S37-46.

2. Teng YK, Verburg RJ, Verpoort KN, Diepenhorst GM, Bajema IM, van Tol MJ, et al. Differential responsiveness to immunoablative therapy in refractory rheumatoid arthritis is associated with level and avidity of anti-cyclic citrullinated protein autoantibodies: a case study. Arthritis research & therapy. 2007;9(5):R106.

3. Suwannalai P, Britsemmer K, Knevel R, Scherer HU, Levarht EW, van der Helm-van Mil AH, et al. Low-avidity anticitrullinated protein antibodies (ACPA) are associated with a higher rate of joint destruction in rheumatoid arthritis. Annals of the rheumatic diseases. 2014;73(1):270-6.

4. Arends EJ, van Dam LS, Kraaij T, Kamerling SWA, Rabelink TJ, van Kooten C, et al. A High-throughput Assay to Assess and Quantify Neutrophil Extracellular Trap Formation. J Vis Exp. 2019(143).