Figure 1. Figure showing the ROC curve for MISA and MISS questionnaires for MTX intolerance (A), Bar diagram showing the prevalence of various symptoms of intolerance in 414 RA patients (B), and Box-and-whiskers plot showing the duration of unpleasant symptoms (C).

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SLE, Sjögren's and APS – treatment

POS0680

BELIMUMAB ADD-ON THERAPY MOBILISES MEMORY B CELLS INTO THE CIRCULATION OF PATIENTS WITH SLE

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Background: Belimumab (BLM), a recombinant human monoclonal antibody directed against B-cell activating factor (BAFF), is the first approved biological agent for patients with active severe systemic lupus erythematosus (SLE) and lupus nephritis (LN). There is clinical evidence that combining BLM with B cell depleting therapy can ameliorate disease activity in severe, refractory SLE patients¹. Although BLM is a B cell directed therapy and has been shown to significantly decrease total B cells, flow cytometry observations suggest a rapid increase of circulating memory B cells (MBC)².

Objectives: To investigate dynamics of B-cell subsets in SLE patients treated with or without BLM, with a focus on assessing MBC characteristics.

Methods: Extensive B cell subset phenotyping was performed by high-sensitivity (HS) flow cytometry (acquisition of 10⁷ leukocytes; per EuroFlow protocols³) on samples from active LN or SLE patients with major organ involvement treated with standard of care (SOC) consisting of high dose steroids and mycophenolate mofetil combined with or without the addition of BLM. MBC gene expression profiles were characterized with single-cell RNA and V(D)J sequencing (ScRNA-SEQ).

Results: By employing HS flowcytometry, we established that the absolute increase in circulating MBC in SLE and LN patients was significant for patients who initiated BLM (Figure 1). The increase was observed in a broad range of MBC subsets (Unswitched, IgG1+, IgG2+, IgA1+, IgA2+) at 2 and 4 weeks following initiation of BLM treatment. This rise in MBC could hypothetically be attributed to either proliferation of blood MBC, BLM induced migration of tissue-resident MBCs or BLM related retention of tissue-destined MBC in the blood. ScRNA-SEQ analysis of cell cycle gene-expression was performed and established in both groups a non-proliferating phenotype [in approximately ~94%] of MBC post-treatment, including absence of MKI67 as active proliferation marker. Clonal diversity analysis comparing week 2 with baseline revealed an unexpected decrease of the largest MBC clones in BLM, whereas no change in clonality was observed with SOC alone. Together these data indicate that proliferation is unlikely to be responsible for the observed increase in MBC by BLM. Furthermore, a clear difference was found in gene-expression levels between both treatment groups:

Figure 1. Change in pre-germinal center and memory B cell counts from baseline to week 4 of patients with SLE or LN treated with SOC (n=8) or SOC+BLM (n=11).

BLM was responsible for the upregulation of 72 vs 10 genes in SOC, likewise 162 vs 32 genes were downregulated. Most importantly, a significant downregulation of the migration genes SELL (CD62L), CCR7, ITGB1, RAC2 and ICAM2, were specifically seen in BLM treated patients. This may reflect disrupted lymphocyte trafficking, preventing MBCs from transmigration from the blood into tissue owing to reduced migration molecules, or preventing MBCs from being retained at the tissue level owing to reduction in tissue adhesion proteins.

Conclusion: The addition of BLM to SOC significantly increases MBCs in patients with SLE independently of proliferation, accompanied by a strong modulation of gene expression, including reduced expression of migration markers pointing towards disrupted lymphocyte trafficking. These data may have important implications for improving treatment strategies in patients with LN or severe SLE, as a deeper depletion of autoreactive MBCs could be established by adding B-cell-depleting therapy after the initiation of BLM.

REFERENCES:

- [1] Arends EJ et al. Long-term effects of combined B cell immunomodulation with rituximab and belimumab in severe, refractory systemic lupus erythematosus: 2-year results. *Nephrol Dial Transplant*. 2020 Jun 27 gfaa117.
- [2] Stohl W et al. Belimumab reduces autoantibodies, normalizes low complement levels, and reduces select B cell populations in patients with SLE. *Arthritis Rheum*. 2012;64(7):2328-2337.
- [3] Blanco et al. Age-associated distribution of B and plasma cell subsets in peripheral blood - *J Allergy Clin Immunol* 2018 141 2208-2219.

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VOCLOSPORIN FOR LUPUS NEPHRITIS: INTERIM ANALYSIS OF THE AURORA 2 EXTENSION STUDY

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Background: Voclosporin, a novel calcineurin inhibitor (CNI), has been tested successfully in two pivotal trials in adult patients with lupus nephritis.

Previously reported results from the Phase 3 AURORA 1 study and the Phase 2 AURA-LV study showed that compared with mycophenolate mofetil (MMF) and low-dose steroids alone, the addition of voclosporin significantly increased the renal response rate and reduced proteinuria, as measured by urine protein creatinine ratio (UPCR), in patients with lupus nephritis (LN) at approximately one year of treatment (48 weeks in AURA-LV and 52 weeks in AURORA 1).

Objectives: Patients that completed one year of treatment in the AURORA 1 study were eligible to enroll into the two-year, blinded, controlled extension study, AURORA 2. Here we report the first interim analysis of the ongoing AURORA 2 study.

Methods: Patients completing AURORA 1 were eligible to continue the same randomized treatment of voclosporin (23.7mg BID) or placebo, in combination with MMF (1 g BID) and low-dose oral steroids in the AURORA 2 extension. This interim analysis evaluated UPCR and estimated glomerular filtration rate (eGFR) in patients with up to two years of total treatment: one year from AURORA 1 and up to one year in AURORA 2.

Results: 116 patients in the voclosporin arm and 100 patients in the control arm enrolled in the extension study, of which 73 patients in the voclosporin arm and 51 patients in the control arm had received two years of treatment at the time of this interim analysis. Mean UPCR at pre-treatment (AURORA 1) baseline was 3.94 mg/mg in the voclosporin arm (n=116) and 3.87 mg/mg in the control arm (n=100). The LS mean change in UPCR from pre-treatment baseline to year two was -3.1 mg/mg for the voclosporin arm (n=73) and -2.1 mg/mg for control arm (n=51; Table 1). Mean eGFR at pre-treatment (AURORA 1) baseline was 79.6 mL/min for the voclosporin arm (n=116) and 78.9 mL/min for the control arm (n=100) and at year two, was 79.0 mL/min for the voclosporin arm (n=73) and 82.9 mL/min for the control arm (n=51). There was a small early decrease in mean eGFR in the first four weeks of treatment (in AURORA 1) after which eGFR remained stable throughout year one and year two. Additionally, there