SAT0164

MC2-03 (CICLOSPORIN EYEDROPS) IMPROVES TEAR PRODUCTION IN SJÖGREN'S PATIENTS WITH MODERATE-TO-SEVERE KERATITIS: RESULTS FROM A PHASE 2B RANDOMIZED, CONTROLLED TRIAL

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Background: Sjögren Syndrome (SS) is a multifaceted disease with variable symptoms, but the SS associated keratoconjunctivitis is one of the most frequent disease manifestations of the syndrome and the manifestation that has the greatest impact on the quality of life for these patients.

Objectives: To report the clinical efficacy of MC2-03 eyedrops in Sjögren's patients with moderate-to-severe keratitis from a 6-month trial looking at the Schirmer score which assesses the tear production by the lacrimal gland. A Schirmer score of ≤ 5 mm/5 min is one of the criteria used in the 2016 final classification of ACR/EULAR to diagnose Sjögren's syndrome.

Methods: The NORTHERN LIGHTS trial is a randomized, double masked, controlled multicentre European trial that assessed MC2-03 eyedrops (ciclosporin 0.03% and 0.06%) for the treatment of moderate-to-severe dry eye disease in 255 patients having corneal fluorescein staining score 3 or 4 at baseline. The Schirmer score (per 5 min) was assessed during this trial. A total of 66 patients (25.9%) with medical history of Sjögren's syndrome were randomized in the trial.

Results: Demographics and baseline disease characteristics were comparable between treatment arms: mean age 60.4 years, 90.9% were females (n=60) and the mean Schirmer score in the worst eye was -3mm (2.8mm - 3.2mm, except for the vehicle, mean Schirmer score of 5.5mm).

The mean Schirmer score improved rapidly from baseline to month 1 for MC2-03 0.03% eye drops (+2.4mm) reaching statistical significance versus vehicle (-0.5mm, p=0.028) and lubricant therapy (-0.6mm, p=0.020). This improvement was maintained at month 6 where the change was +2.5mm for MC2-03 0.03% eye drops compared to -1.1mm for vehicle (p=0.028). Statistical significance was also achieved at Month 6 comparing the higher strength MC2-03 0.06% eye drops (+2.8mm) to vehicle (-1.1mm, p=0.005) and lubricant alone (-0.5mm, p=0.009).

Three in eleven (27.3%) Sjögren's patients treated with MC2-03 0.03% eye drops improved from a diagnostically low Schirmer ≤ 5 mm at baseline (10/12, 83.3% ≤ 5 mm) to Schirmer > 5 mm at month 3 and month 6 (6/11, 54.5% ≤ 5 mm), while on the other hand 1 in 14 (7.1%) patients worsened in the vehicle group. A similar response was seen for MC2-03 eye drops 0.06%.

For Sjögren's patients with Schirmer ≤ 5 mm at baseline, a greater proportion of patients improved ≥ 3 mm at month 6 when treated with MC2-03 eye drops 0.03% (44.4%, 4/9) and 0.06% (53.8%, 7/13) compared to vehicle (0%, 0/9) and lubricant (7.7%, 1/12). At month 6, a statistically significantly higher proportion of patients achieved clinically meaningful improvements in both corneal staining (≥ 2 grades improvement) and Schirmer score (≥ 3 mm/5 min) when treated with MC2-03 0.03% eye drops (45.5%, 5/11) compared to both vehicle (0%, 0/14, p=0.009) and lubricant (0%, 0/15, p=0.007). A higher number of patients treated with MC2-03 0.06% was observed without statistical significance.

Conclusion: MC2-03 eye drops once daily rapidly increased tear production and further improved corneal staining in Sjögren's patients with moderate to severe keratitis, which both are objectives included as diagnostic criteria for Sjögren's disease. MC2-03 eye drops were well tolerated with no unexpected safety findings.

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SAT0165

PRECLINICAL AND CLINICAL CHARACTERIZATION OF CENERIMOD, A POTENT, SELECTIVE, AND ORALLY ACTIVE SPHINGOSINE-1-PHOSPHATE RECEPTOR 1 MODULATOR IN SLE

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Background: SLE is an autoimmune disease characterized by aberrant lymphocyte activation and autoantibody production. In SLE, autoreactive lymphocytes migrate from lymphoid organs into the blood, and subsequently into tissue. This leads to systemic and multiorgan inflammation and pathology resulting in significant morbidity and mortality. Lymphocyte migration is a tightly controlled process driven by chemokine gradients. The chemotactic gradient across the vascular barrier established by sphingosine-1-phosphate (S1P) orchestrates egress of lymphocytes out of peripheral lymphoid organs into the blood. Cenerimod is a potent, selective, and orally active S1P receptor 1 (S1P₁) receptor modulator that induces receptor internalization and thereby prevents lymphocyte egress from lymphoid organs into the blood [1].

Objectives: In-depth preclinical and clinical characterization of cenerimod in modulating SLE.

Methods: Lymphocytes from patients with SLE and healthy subjects were assessed for cenerimod-induced S1P₁ receptor internalization. Efficacy of cenerimod was evaluated in the MRL/lpr lupus mouse model. In a 12-week phase 2 clinical trial in patients with SLE treated with multiple doses of cenerimod (NCT02472795), lymphocyte subsets and inflammatory biomarkers were characterized.

Results: Cenerimod was potent and efficacious at inducing S1P₁ receptor internalization in T and B lymphocytes with an EC₅₀ of 15 nM in both healthy subjects and patients with SLE. In lupus-like MRL/lpr mice treated with cenerimod, circulating T and B lymphocytes were reduced, which resulted in reduced immune infiltrates into tissue, reduced autoantibody production and inflammation, decreased proteinuria, and increased survival. In patients with SLE treated with cenerimod for 12 weeks, a dose-dependent reduction of circulating T cells (95%), B cells (90%), and antibody-secreting cells (85%) was evident. Furthermore, a reduction in anti-dsDNA antibodies and IFN- α , associated with an inflammatory phenotype, was observed.

Conclusion: Cenerimod was potent and efficacious in reducing S1P₁ receptor surface expression on lymphocytes *in vitro*, and in reducing circulating T and B lymphocyte populations, including antibody-secreting cells, and in decreasing inflammatory biomarkers in patients with SLE *in vivo*. Furthermore, cenerimod significantly ameliorated systemic and organ-specific autoimmunity in a mouse model of SLE. These results support the further investigation of the clinical efficacy and safety of cenerimod in the ongoing phase 2b clinical trial (NCT03742037).

References:

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BIOMARKERS OF B-CELL DEPLETION AND RESPONSE IN A RANDOMIZED, CONTROLLED TRIAL OF OBINUTUZUMAB FOR PROLIFERATIVE LUPUS NEPHRITIS

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Background: Incomplete B-cell and plasmablast depletion, as measured using highly sensitive flow cytometry (HSFC), is associated with lower response rates following rituximab in SLE [1]. Enhanced B-cell depletion with the type II anti-CD20 mAb obinutuzumab resulted in increased renal responses in proliferative lupus nephritis (LN) in the NOBILITY trial (NCT02550652) and will be further evaluated in the Phase 3 REGENCY trial (NCT04221477).

Objectives: To measure peripheral B-cells, B-cell subsets (naïve, memory and plasmablast) and B-cell activating factor (BAFF) levels and to assess associations between B-cell depletion and renal response in LN patients in a clinical trial of obinutuzumab.

Methods: 126 patients with active Class III/IV LN were randomized to obinutuzumab or placebo infusions in combination with mycophenolate and glucocorticoids. Peripheral B-cells were measured using a HSFC method with a lower limit of quantitation of 0.441 cells/μL. Serum levels of BAFF were evaluated using ELISA. Sustained depletion was defined by total B-cells below the limit of detection at both weeks 24 and 52. Renal response definitions from Phase 2 NOBILITY and Phase 3 REGENCY trials were used.

Results: Obinutuzumab resulted in rapid and complete depletion of total B-cells, memory and naïve B-cells, and plasmablasts from peripheral blood, with 88% of obinutuzumab patients depleted to < 0.441 total B-cells/μL at week 2 (Figure). Mean serum BAFF increased from 4,585 pg/mL at baseline to 14,601 pg/mL at week 52 in the obinutuzumab group. Sustained B-cell depletion was achieved in 32/52 (62%) of patients with complete data and was associated with higher renal response rate at week 76 (Table), although patients who achieved sustained depletion also had lower baseline proteinuria and serum creatinine.

Conclusion: Obinutuzumab, a type II anti-CD20 mAb, mediated rapid, complete and sustained depletion of peripheral B-cells and plasmablasts and large increases in serum BAFF. Similar to previous reports, sustained B-cell depletion was associated with increased renal response though there may be confounding factors. REGENCY is being conducted to further evaluate the therapeutic hypothesis with obinutuzumab in LN.

References:

[1] Md Yusuf MY et al. *Ann Rheum Dis*. 2017;76:1829-36.

Figure. Mean levels of selected biomarkers over time by treatment group

MMF, mycophenolate mofetil.
Error bars represent 95% confidence intervals for the mean.

Table. Data from NOBILITY at week 76 by depletion status at weeks 24 and 52

Definition of response	Obinutuzumab sustained depletion (N = 32) ^a	Obinutuzumab detectable B-cells (N = 20) ^a	Placebo group detectable B-cells (N = 62)
NOBILITY complete response UPCR < 0.5, SCr ≤ ULN and not increased > 15% from baseline SCr, and < 10 RBC/hpf without casts	50%**	35%*	18%
NOBILITY overall response CRR or ≥ 50% reduction in UPCRb with SCr not increased > 15% from baseline and urinary RBCs not increased > 50% from baseline	66%***	45%*	29%
REGENCY complete response UPCR < 0.5, SCr ≤ ULN and not increased > 25% from baseline SCr	69%**	45%	31%
REGENCY overall response CRR or ≥ 50% reduction in UPCRb with SCr not increased > 25% from baseline	84%***	55%	50%

* P < 0.2 vs. placebo group.

** P < 0.05 vs. placebo group.

*** P < 0.001 vs. placebo group.

^a Eleven patients in the obinutuzumab group with insufficient data to determine depletion status were excluded.

^b ≥ 50% reduction in UPCR to a value < 1 (< 3 if the baseline UPCR was ≥ 3).

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SAT0167 RACIAL DIFFERENCES IN THE IMPACT OF HYDROXYCHLOROQUINE ON IMMUNOLOGIC MARKERS IN SLE PATIENTS

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Background: In patients with Systemic Lupus Erythematosus (SLE), Hydroxychloroquine (HCQ) treatment has been associated with reduced disease activity, lower rates of certain forms of organ damage, and improved survival¹.

Objectives: To gain insight into the mechanisms involved, we examined the impact of HCQ treatment on immunologic biomarkers that have been associated with higher rates of organ damage. These include lupus anticoagulant, anti-dsDNA, low complement, and anticardiolipins (aCL).

Methods: We analyzed retrospective data on more than 56,000 quarterly clinic visits from more than 1000 patients in a large American clinical cohort of SLE patients. Patients visits were classified as "on HCQ" if they reported taking HCQ at that visit and at the previous visit. Patient visits were classified as "off HCQ" if they reported not taking HCQ at that visit and at the previous visit. For each patient, visits on and off HCQ were compared with respect to the rates of biomarker positivity. These comparisons were summarized across patients using conditional logistic regression controlling for age.

Results: Table 1 shows the results of our analyses. While on HCQ, the odds of being positive was significantly reduced for each biomarker: Lupus Anticoagulant (OR= 0.65), antidsDNA (OR=0.82), Low Complement (OR=.71), aCL IgG (OR=0.26), and aCL IgM (OR=0.45). However, there was a substantial difference between Caucasian Americans (CAs) and African Americans (AAs) with respect to the impact of HCQ. Notably, HCQ was associated with a 62% reduction in the odds of lupus anticoagulant among CAs, but no association was observed among AAs.