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OP0235 A NOVEL B CELL SPECIFIC IFN-I BIOMARKER IS ASSOCIATED WITH PLASMA BLAST NUMBERS FOLLOWING B CELL DEPLETION THERAPY IN SLE

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Background: SLE is a Type I interferon (IFN-I) mediated disease with autoreactive B cells. Plasmablasts, the immediate progeny of B cells, are expanded in SLE and correlate with disease activity. We showed that their rate of regeneration after therapeutic B cell depletion with rituximab is variable and predicts relapse[1]. IFN-I has been shown *in vitro* to induce the differentiation of B cells into plasmablasts. We previously showed that therapeutic B cell depletion with anti-CD20 mAb leads to a transient reduction in CD20-negative plasmablasts, following which plasmablasts repopulate and their numbers predict clinical relapse. We developed tethrin as a flow cytometric, cell-specific marker for IFN-I response.

Objectives: To test the hypothesis that memory B cell tethrin determines the rate of plasmablast repopulation after rituximab.

Methods: 117 rituximab-treated SLE patients were studied prospectively using BILAG-2004 and flow cytometry. In 97 responders we tested plasmablasts at 6 months as a predictor of clinical relapse before 12 months to validate our previous finding. In 50 patients pre-rituximab and 28 patients post-rituximab we performed additional flow cytometry to measure tethrin on each cell subset. Expression of 18 ISGs was measured using Taqman on PBMCs and an ISG score calculated.

Results: We divided clinical responders to rituximab into earlier relapse (12 months) or later relapse (>12 months). As in our published discovery cohort, plasmablasts were strongly predictive of clinical relapse. ROC analysis indicated that a plasmablast count of $>0.0008 \times 10^9/L$ at 6 months yielded 73% (95% CI 45–92%) sensitivity and 90% (95% CI 56–99%) specificity in predicting earlier relapse; area under the curve of 0.86.

Plasmablast numbers after rituximab were associated with Memory B cell tethrin ($R=0.38$, $p=0.047$) but not ISG score ($R=0.24$, $p=0.219$) (Table 1).

In Pre-rituximab there was no relationship between any IFN assay and plasmablast count. After rituximab treatment there was no correlation between plasmablast count and ISG expression, nor with monocyte or NK cell surface tethrin. However, memory B cell tethrin MFI was positively correlated with plasmablast count (Table 1).

Table 1

Interferon assay	Plasmablast Count (cells $\times 10^9/L$)	
	Pre-rituximab (n=50)	Post-rituximab (n=28)
ISG expression Score:	-0.11, $P=0.448$	0.24, $P=0.219$
Tethrin protein level: Monocytes	-0.08, $P=0.592$	0.20, $P=0.296$
T-cells	-0.16, $P=0.269$	0.32, $P=0.096$
NK cells	-0.14, $P=0.324$	0.05, $P=0.795$
Naïve B-cells	-0.04, $P=0.801$	0.30, $P=0.121$
Memory B-cells	0.07, $P=0.618$	0.38, $P=0.047$

Values are Spearman's Rank Correlation Coefficient and P values.

Conclusions: Although interferon stimulated gene expression is commonly used to measure IFN-I activity, tethrin provides a cell-specific assay. We demonstrate that by measuring IFN-I response in B cells specifically, we could explain plasmablast differentiation, and thereby clinical outcome. Memory B cell tethrin is valuable to immunophenotype SLE.

References:

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OP0236 BENEFIT AND SAFETY OF ANTITHROMBOTIC TREATMENT IN 264 PREGNANCIES IN PATIENTS WITH ANTIPHOSPHOLIPID SYNDROME

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Background: The management of pregnancy in patients with antiphospholipid syndrome (APS) with aspirin and heparin is based on empiric recommendations. **Objectives:** Our study aimed to evaluate the outcomes of treated patients with thrombotic and obstetric APS and the safety of antithrombotic treatments prescribed during pregnancy.

Methods: Inclusion criteria were (1) APS (Sydney criteria), (2) live pregnancy at 12 weeks of gestation (WG) with (3) follow up data until 6 weeks post-partum. Data were collected prospectively (PROMISSE study) and retrospectively (four French centers). Adverse pregnancy outcomes (APOs) were defined by fetal death or neonatal death; pre-term delivery before 36 WG due to preeclampsia or placental insufficiency; or small for gestational-age (SGA; <5th percentile). Major bleeding was defined as blood loss greater than 500mL and/or requiring surgery or transfusion.

Results: 264 pregnancies (87 collected prospectively) in 204 patients were included (46% with a history of thrombosis, and 23% with associated systemic lupus erythematosus). During pregnancy, treatment included heparin (n=253; 96%) and low-dose aspirin (n=223; 84%).

The live birth rate was 86%. APOs occurred in 32%, mostly during the 2nd trimester: fetal deaths 11%, SGA 11%, pre-term delivery before 36 WG due to preeclampsia or placental insufficiency 17%. Thirteen maternal thrombotic events occurred in 12 (4.5%) pregnancies. Forty-six maternal hemorrhagic events occurred in 40 (15%) pregnancies (30 events in the post-partum period). Major bleeding was reported in only 6 pregnancies (2.3%) and occurred only after delivery. Except for two events, post-partum hemorrhage occurred in the early post-partum before hospital discharge. No maternal death was observed.

Aspirin therapy during pregnancy was the only independent factor associated with a lower risk of APOs (odds ratio: 0.34; 95% CI: 0.15 – 0.78; $p=0.01$) in multivariate analysis.

Neither heparin or aspirin alone, nor combined therapy increased the risk of hemorrhage. In the retrospective cohort, emergency caesarian section was the only factor associated with hemorrhagic events during the study period (53% hemorrhages in patients who underwent emergency caesarian compared to 18%, $p=0.005$). Independent risk factors for APOs were elevated body mass index and the presence of lupus anticoagulant.

Conclusions: We report a high level of obstetrical complications in conventionally-treated APS pregnancies, and a beneficial effect of addition of aspirin to prevent obstetrical morbidity. Moreover, heparin and aspirin were well tolerated and did not increase risk of hemorrhage.

Disclosure of Interest: None declared

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OP0237 LIFITEGRAST OPHTHALMIC SOLUTION 5.0% FOR TREATMENT OF DRY EYE DISEASE: COMBINED EVIDENCE FROM 5 RANDOMIZED CONTROLLED TRIALS

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Background: Dry eye disease (DED) is a multifactorial disease of the tear film and ocular surface, characterized by ocular discomfort and visual disturbance.¹ DED is associated with a number of systemic autoimmune diseases, particularly rheumatoid arthritis and Sjögren's syndrome.^{2,3} Lifitegrast is a lymphocyte function-associated antigen-1 (LFA-1) antagonist that inhibits T-cell-mediated inflammation (an underlying factor in DED) and is approved in the US for the treatment of signs and symptoms of DED (lifitegrast ophthalmic solution 5.0%, Xiidra®).

Objectives: To evaluate the combined evidence from 5 clinical trials of lifitegrast ophthalmic solution 5.0% (LIF) in subjects with dry eye disease (DED).

Methods: Adults with DED were randomized to LIF or placebo (PBO) in 5 randomized, double-masked, placebo-controlled trials: 4 12-week efficacy/safety studies (phase 2, LIF n=58, PBO n=58; phase 3 trials: OPUS-1, LIF n=293, PBO n=295; OPUS-2, LIF n=358, PBO n=360; OPUS-3, LIF n=355, PBO n=356), and a 1-year safety study (SONATA, LIF n=220, PBO n=111). Individuals with secondary Sjögren's syndrome associated with autoimmune disease (eg, rheumatoid arthritis, systemic lupus erythematosus) were eligible to participate if they were not immunodeficient/immunosuppressed, not taking steroids, and met all other inclusion and exclusion criteria. Change from baseline to day 84 in DED signs and symptoms was evaluated across the 12-week studies. Key measures were inferior corneal staining score (ICSS; 0–4 scale), eye dryness score (EDS; visual analogue scale [VAS], 0–100 scale), and visual-related function subscale of a symptom scale (0–4 scale). Pooled safety data (LIF n=1287, PBO n=1177) from all 5 trials were also analyzed.

Results: LIF improved ICSS versus PBO in the phase 2 study (secondary endpoint; treatment effect 0.35, nominal $P=0.0209$), OPUS-1 (co-primary; 0.24,

Key efficacy results of lifitegrast ophthalmic solution 5.0% across 12-week multicenter randomized controlled trials (ITT population with LOCF)

Study	Symptom endpoint	Sign endpoint
Phase 2	<ul style="list-style-type: none"> Visual-related function subscale (secondary, change from baseline to day 84): TE 0.37, nominal $P=0.0394$. 	<ul style="list-style-type: none"> Primary endpoint of ICSS at day 84: not met. ICSS (secondary, change from baseline to day 84): TE 0.35, nominal $P=0.0209$.
OPUS-1	<ul style="list-style-type: none"> Coprietary endpoint of change from baseline to day 84 on visual-related function subscale not met. 	<ul style="list-style-type: none"> ICSS (co-primary, change from baseline to day 84): TE 0.24, $P=0.0007$.
OPUS-2	<ul style="list-style-type: none"> EDS (VAS; co-primary, change from baseline to day 84): TE 12.61, $P<0.0001$. 	<ul style="list-style-type: none"> Coprietary endpoint of change from baseline to day 84 in ICSS not met.
OPUS-3	<ul style="list-style-type: none"> EDS (VAS; primary, change from baseline to day 84): TE 7.16, $P=0.0007$. 	<ul style="list-style-type: none"> ICSS (ad hoc, change from baseline to day 84): TE 0.17, nominal $P=0.0144$.

Eye dryness score (EDS; visual analogue scale [VAS]); ICSS, inferior corneal staining score; ITT, intention-to-treat; LOCF, last observation carried forward; TE, treatment effect.

$P=0.0007$), and OPUS-3 (ad hoc; 0.17, nominal $P=0.0144$). LIF reduced EDS (VAS) versus PBO in OPUS-2 (co-primary; 12.61, $P<0.0001$) and OPUS-3 (primary; 7.16, $P=0.0007$). The OPUS-1 co-primary symptom endpoint of visual-related function subscale, and the OPUS-2 co-primary sign endpoint of ICSS, did not achieve statistical significance. In the pooled safety analysis, total exposure was 415.65 person-years for LIF, and 332.15 person-years for PBO. Adverse events were mostly mild or moderate in severity. There were no serious ocular treatment-emergent adverse events (TEAEs) and withdrawals due to TEAEs were infrequent (LIF, 7.0%; PBO, 2.6%).

Conclusions: LIF improved signs and symptoms of DED in adults with DED and appeared to be well tolerated with no serious ocular TEAEs reported.

References:

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LB0002 48 WEEK COMPLETE REMISSION OF ACTIVE LUPUS NEPHRITIS WITH VOCLOSPORIN

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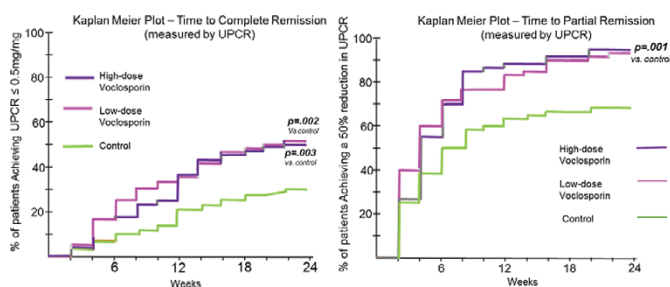
Background: Voclosporin (VCS) is a novel CNI intended for use in the treatment of autoimmune diseases such as lupus nephritis (LN). VCS's unique structure allows for less pharmacokinetic-pharmacodynamic variability and a potentially improved safety profile compared to other CNIs.

Objectives: Achievement of complete remission (CR) as assessed at week 24 (primary objective) and assessment of the efficacy over 48 weeks (secondary objective), with 2 doses of VCS (low dose VCS: 23.7mg BID and high dose VCS: 39.5mg BID) vs. placebo in subjects with active LN.

Methods: The double blind placebo controlled AURA study enrolled 265 subjects with active LN in 20 countries. Patients were randomized into 3 arms (placebo, low dose VCS or high dose VCS) in addition to MMF 2g/day and steroids (with rapid tapering). CR was defined as a confirmed urine protein/creatinine ratio (UPCR) of ≤ 0.5 mg/mg using first morning void and confirmed estimated glomerular filtration rate (eGFR, CKD-EPI equation) ≥ 60 mL/min/1.73 m² or no decrease from baseline in eGFR of $\geq 20\%$ in the presence of low dose steroids. Partial remission (PR) was defined as a 50% reduction in UPCR. UPCR assessments were made at each visit, together with biomarker data at regular intervals.

Results: We now present the 48 week data showing improved CR rates over the 24 week data. The rate of CR was significantly higher in the low dose VCS compared to the control group (32.6% vs. 19.3%; OR: 2.03, $p=0.045$) at 24 weeks. It was 27.3% in the high dose VCS group ($p=NS$). Both doses of voclosporin demonstrated superiority to control using time to CR, PR (50% reduction in proteinuria) and time to PR.

At 48 weeks, 23.9% of patients on the control arm achieved CR compared to 49.4% low dose (OR: 3.21, $p<0.001$) and 39.8% high dose (OR: 2.10, $p<0.026$). Over 92% of subjects experienced at least one adverse event (AE) with the most common two being infections (58% low, 66% high and 55% placebo) and GI disorders (43% low, 52% high and 38% placebo). The overall rate of serious adverse events (SAEs) was numerically higher in both voclosporin groups (28% low, 25% high, 19% placebo) with the nature of SAEs consistent with those observed in patients with highly active LN. Most deaths occurred in the first 2 months and were: low dose (infection3, ARDS2, thrombotic3, cardiac tamponade, pulmonary hemorrhage), high dose (infection, PE) and control (CVA). All were considered unrelated to drug exposure by the investigators. 3 additional deaths occurred in placebo patients after the conclusion of the 48 weeks of treatment.



Conclusions: The AURA-LV study is the first global study demonstrating the beneficial effect of VCS, in combination with MMF and steroids, in the treatment of LN. Remission rate was rapid. VCS treatment resulted in increasing CR and PR seen by week 6 despite rigorous steroid taper (mean steroid dose 4 mg at week 16). Adverse events were higher in the treated patient group with the nature in keeping with immunosuppression. These promising data will be used to plan subsequent studies of voclosporin in LN.

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Axial spondyloarthritis from risk factor to clinical outcomes

OP0238 MEASUREMENT OF SPINAL MOBILITY IN AXIAL SPONDYLOARTHRITIS USING INERTIAL SENSORS: RELIABILITY AND VALIDATION PRELIMINARY RESULTS

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Background: Axial spondyloarthritis (axSpA) is a chronic rheumatic disease that causes reduction of mobility in the patients' spine. There are several indices to analyze this mobility: BASMI, which lacks precision and sensitivity to change according to different authors, and UCOASMI (1) based on motion capture, which needs extensive resources that limit its practical applicability. Inertial measurement unit sensors (IMU) give, in real time, the 3D orientation of any anatomical place