plus SST. Primary endpoints: safety assessments. Key secondary endpoints: SRI4 response rate at each scheduled visit (observed data), defined as a ≥ 4 -point reduction from baseline in SELENA-SLEDAI score, no worsening in PGA (< 0.3 -point increase from baseline) and no new BILAG 1A/2B organ domain scores; time to first severe SFI flare over time. Endpoints were analysed relative to first BEL dose (parent or current study). No follow-up data were collected after study withdrawal.

Table.

Endpoint, n (%)	Anytime post baseline N=142	Year 0-1 n=142	Year 1-2 n=136	Year 2-3 n=108	Year 3-4 n=79	Year 4-5 n=32	Year 5-6 n=24	Year 6+ n=13
≥ 1 AE	139 (97.9)	133	122	81	59	30	24 (100)	9
≥ 1 severe AE	27 (19.0)	(93.7)	(89.7)	(75.0)	(74.7)	(93.8)	1 (4.2)	(69.2)
		12 (8.5)	10 (7.4)	7 (6.5)	2 (2.5)	1 (3.1)		0
≥ 1 treatment-related AE	81 (57.0)	46 (32.4)	38 (27.9)	20 (18.5)	11 (13.9)	9 (28.1)	3 (12.5)	1 (7.7)
≥ 1 SAE	48 (33.8)	24 (16.9)	18 (13.2)	9 (8.3)	6 (7.6)	2 (6.3)	3 (12.5)	0
Serious infections and infestations	24 (16.9)	14 (9.9)	5 (3.7)	2 (1.9)	3 (3.8)	0	1 (4.2)	0
Deaths	1 (0.7)*	0	0	0	0	0	0	0
AESI								
Malignancy	1 (0.7)	0	1 (0.7)	0	0	0	0	0
Opportunistic infections	10 (7.0)	3 (2.1)	4 (2.9)	1 (0.9)	1 (1.3)	0	0	0
Post-infusion systemic reactions	20 (14.1)	7 (4.9)	4 (2.9)	4 (3.7)	2 (2.5)	5 (15.6)	1 (4.2)	0
Depression/suicide/self-injury†	9 (6.3)	4 (2.8)	2 (1.5)	1 (0.9)	1 (1.3)	0	0	0

*Death from an AE of endocarditis that began ~1 month after the exit visit; the investigator considered it to be unrelated to the study drug

†No serious suicide/self-injury AEs were reported during the study

Results: Overall, 142 pts were enrolled (Japan n=72; Korea n=70), 104 (73.2%) completed the study, 1 (0.7%) died and 37 (26.1%) withdrew.

Overall, 139 (97.9%) pts had ≥ 1 adverse event (AE) (Table). Most frequent AEs included: nasopharyngitis (60.6%); headache (28.2%); cough, herpes zoster and viral upper respiratory tract infection (18.3% each). Serious AEs (SAEs) occurred in 48 (33.8%) pts. Most common SAEs were infections and infestations, reported in 24 (16.9%) pts (Table). During this study, the annual incidence of AEs, including SAEs and AESI, remained stable or declined, with no trends of clinical concerns regarding the incidence of Grade 3 or 4 values for laboratory parameters. There was 1 transient positive immunogenicity result of no clinical concern.

The proportion of SRI4 responders was 47.8% at Year 1 (Week 24) and tended to increase numerically up to 84.6% at Year 7 (Week 48). The proportion of pts with a ≥ 4 -point decrease from baseline in SELENA-SLEDAI score numerically increased from 51.5% at Year 1 (Week 24) to 84.6% at Year 7 (Week 48). Proportion of pts with no PGA worsening was 91.3-100% and the proportion with no new BILAG 1A/2B organ domain scores was 93.3-100% up to Year 7 (Week 48). A total of 21 (14.8%) pts had 24 severe SFI flares.

Conclusion: BEL was well tolerated as add-on therapy to SST for ≤ 7 years in pts with SLE from Japan/Korea. Safety results were consistent with the known BEL safety profile.

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SAT0194

LACK OF EFFICACY OF RIVAROXABAN IN THE TREATMENT OF ANTIPHOSPHOLIPID SYNDROME AND CLINICAL SIGNIFICANCE OF ANTIPHOSPHOLIPID ANTIBODIES

S. Vardanyan¹, K. Ginosyan², V. Vardanyan¹, A. Sargsyan², A. Simonyan².
¹"Mikaelyan" Institute of Surgery, Yerevan, Armenia; ²Yerevan State Medical University, Yerevan, Armenia

Background: Chronic anticoagulation with vitamin K antagonists (VKA) is the standard treatment to prevent thrombotic events in antiphospholipid syndrome (APS). But in recent years treatment schemes began to include rivaroxaban. Use of direct oral anticoagulants (DOAC) is an attractive and often preferred alternative to VKAs in other medical settings owing to greater ease of use, fewer food and drug interactions, and lower bleeding risks [1]. However, according to last guidelines, rivaroxaban should not be used in patients with triple aPL positivity due to the high risk of recurrent events [2].

Objectives: 1. To determine the risk of recurrent thrombosis in single or double positive APS patients treated with rivaroxaban.

2. Find out possible association between presence of particular antiphospholipid antibodies or high level of lupus anticoagulant (LA) and type of vascular events.

Methods: 33 patients with confirmed APS (25 female (75.8%), 8 male (24.2%), mean age 43.2 $\pm$ 11.6 years) were included in the study. 17 (51.5%) of investigated patients had primary APS, in remaining 16 (48.5%) APS was included in the framework of SLE. 18 (54.5%) patients were treated with warfarin 2.5-7.5 mg/daily, 15 (45.5%) patients - with rivaroxaban 20mg/daily for a follow-up period of 12 months. The data is introduced as odds ratios (OR) with 95% confidence interval (CI). The results were considered significant when p < 0.05.

Results: At baseline 21 (63.6%) patients had history of arterial thrombosis, 10 (30.3%) - venous thrombosis, 17 (51.5%) - pregnancy loss. According to results of serum immunology check, 29 (87.9%) patients were anticardiolipin antibody (ACA) positive, 9 (27.3%) - LA positive, 19 (57.6%) - anti- $\beta 2$ -glycoprotein antibodies (anti- $\beta 2$ -gp) positive; 20 (60.6%) patients were double positive (12 (36.4%) of them had positive ACA and anti- $\beta 2$ -gp, 6 (18.2%) - ACA and LA, and 2 (6.1%) - anti- $\beta 2$ -gp and LA), 4 (12.1%) patients were triple positive.

No association between vascular event and/or pregnancy loss in patients with single positive ACA was found. We have found positive association between arterial thrombosis and single positive anti- $\beta 2$ -gp (OR /CI 95% / = 5.0 /2.08 – 23.06/, p < 0.05), positive association between positive LA and venous thrombosis (OR /CI 95% / = 10 /1.7-57.7/, p < 0.05), strong positive association between positive LA and thromboembolism of pulmonary artery (OR /CI 95% / = 46.0 /4.0-525.1/, p < 0.001), negative association between positive LA and pregnancy loss (OR /CI 95% / = 0.06 /0.03 – 0.1/, p < 0.01).

Risk of thrombosis and/or pregnancy loss was not significantly increased in double positive patients, but triple positive patients had increased risk of venous thrombosis (OR /CI 95% / = 9.4 /3.2 – 105.8/, p < 0.04).

Recurrent thrombosis was detected in 16 patients: 2 patients (12.5%) were on warfarin, 14 (87.5%) - on rivaroxaban (10 (71.4%) arterial thrombosis, 4 (28.6%) venous thrombosis).

No association between warfarin 2.5-7.5 mg/daily and occurrence of recurrent thrombosis was detected. An association between use of warfarin and increased risk of bleeding was found, but the risk was not significant (OR /CI 95% / = 7.0 /0.7 – 66/, p = 0.09). Rivaroxaban 20 mg/daily was associated with recurrent thrombosis not only for triple positive patients (p < 0.02), but also in double positive patients (OR /CI 95% / = 21.3 /1.8 – 251/, p < 0.04).

Conclusion: Rivaroxaban does not prevent recurrent thrombosis not only in triple positive patients, but also in single and double positive APS patients. Type of antiphospholipid antibodies can be predictive for the type of further vascular event.

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SAT0195

ABNORMALITY TFH SUBSETS INDICATE DISEASE ACTIVITY WHILE SIROLIMUS THERAPY RESTORES THE PD-1/ICOS+TFH/ACTIVATED TFR BALANCE IN PRIMARY SJOGREN'S SYNDROME PATIENTS

Y. Wang¹, J. Luo¹, C. Gao², X. C. Zhao¹. ¹The Second Hospital of Shanxi Medical University, Taiyuan, China; ²Brigham and Women's Hospital, Boston, United States of America

Background: Immune imbalance between follicular helper T (Tfh) cells and follicular regulatory T (Tfr) cells is a characteristic of primary Sjogren's syndrome (pSS) [1]. The heterogeneity among Tfh and Tfr can be elucidated by separating them into different subsets based on the expression molecular characteristics.

Objectives: The aim of this study was to investigate the role of Tfh and Tfr subsets, and to evaluate the effects of sirolimus on these cells.

Methods: In this study, we enrolled 51 pSS patient and 26 healthy controls (HCs), and analyzed the frequencies and absolute counts of circulating Tfh and Tfr subsets, and serum levels of cytokines. Within these patients, analyses of above T

cells in twelve patients before and after treatment with sirolimus. Clinical indicators and correlations with follicular T cells were systematically analyzed. The diagnostic value for CD4+CXCR5+T cells was evaluated by the areas under the receiver operating characteristic curves (AUC).

Results: Patients with pSS had higher frequencies and absolute numbers of PD-1+ICOS+Tfh cells, but lower levels of activated Tfr cells, thereby resulting in elevated ratios of PD-1+ICOS+Tfh/activated Tfr. In addition, PD-1+Tfh cells levels were lower in pSS patients than in HCs. Interestingly, the ratio of PD-1+ICOS+Tfh/activated Tfr was a strong predictor of pSS diagnosis. However, sirolimus therapy resulted in significant reductions in PD-1+ICOS+Tfh cells and the PD-1+ICOS+Tfh/activated Tfr ratio in pSS patients. We also found increased numbers of PD-1+ICOS+Tfh cells were associated with B cells, while decreased numbers of Tfr and their subsets were strongly associated with aTreg cells in pSS patients. The ESSDAI [2] was positively correlated with PD-1+ICOS+Tfh cell frequency, but was negatively correlated with PD-1+Tfh cell count.

Conclusion: These findings suggest that the PD-1+ICOS+Tfh cell:activated Tfr cell ratio and PD-1+Tfh cells constitute potential novel biomarkers for pSS, and Tfr cells and subsets resemble derived aTreg cells. Furthermore, the PD-1+ICOS+Tfh cells as a biomarker of disease activity and provide new ground to verify the therapeutic implications of sirolimus as an innovative drug in pSS.

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SAT0196 A DOUBLE BLIND, PLACEBO CONTROLLED, SINGLE ASCENDING DOSE (SAD) AND MULTIPLE ASCENDING DOSE (MAD) STUDY OF ALPN-101, A FIRST-IN-CLASS DUAL ICOS/CD28 ANTAGONIST, IN HEALTHY VOLUNTEERS (HV)

J. Yang¹, J. Hillson¹, J. Lickliter², K. Manjarrez¹, A. Tercero¹, J. Wiley¹, G. Means¹, R. Sanderson¹, K. Carley¹, S. L. Peng¹. ¹Alpine Immune Sciences Inc, Seattle, United States of America; ²Nucleus Network, Melbourne, Australia

Background: ALPN-101 (ICOSL vIgD-Fc) is an Fc fusion protein of a human inducible T cell costimulatory ligand (ICOSL) variant immunoglobulin domain (vIgDTM) designed to inhibit simultaneously the CD28 and ICOS inflammation pathways (1). ALPN-101 is effective in preclinical studies of lupus, arthritis, and Sjögren's, and shows greater activity than single pathway inhibitors (2,3,4). It is in development for the treatment of multiple rheumatic and other inflammatory diseases.

Objectives: To evaluate the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of ALPN-101 in HV

Methods: This was a first-in-human study of ALPN-101 (NCT03748836). 72 HV were allocated 4:2 to single intravenous (IV) or subcutaneous (SC) doses of ALPN-101: placebo at 0.001 – 10 mg/kg; 24 HV were allocated 6:2 to repeated IV doses of up to 1 mg/kg weekly x 4. Subjects were followed for 28 (SAD) or 49 (MAD) days to assess safety, PK, target saturation (TS) on T cells, circulating cytokines and PD, the latter based on suppression of IgG responses to keyhole limpet hemocyanin (KLH).

Results: ALPN-101 was generally well-tolerated, with no treatment related serious adverse events, no cytokine release, no clinical immunogenicity, and no adverse trends in safety laboratories. Overall, adverse events were reported in 74.2% of subjects on ALPN-101 and 66.7% of subjects on placebo. All events were mild or moderate and resolved without sequelae. Dose-dependent increase in ALPN-101 exposure was observed from 0.012 to 10 mg/kg. The estimated $t_{1/2}$ was 2-8.6 days over 0.3 – 10 mg/kg. SC bioavailability was ~60% at 3 mg/kg. Minimal to modest accumulation was observed with repeat IV dosing. The TS at C_{max} increased with dose between 0.001–0.03 mg/kg; thereafter the duration of high level TS (>95%) increased with dose (Figure 1). The duration of suppression of IgG anti-KLH response paralleled the duration of high level TS (Figure 2).

Figure 1. Mean + SD Target Saturation of ALPN-101 on Circulating CD4+T Lymphocytes

Figure 2. Mean + SD Serum Anti-KLH IgG Change Relative to Baseline

Conclusion: ALPN-101 was well tolerated when administered as single doses up to 10 mg/kg or as repeated doses of up to 1 mg/kg weekly for 4 weeks, exhibiting dose-dependent PK, TS and PD including the inhibition of antibody responses to KLH immunization. These findings support future studies to evaluate the efficacy of ALPN-101 in multiple rheumatic and other inflammatory diseases.

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