have a poor renal prognosis. Early subtypes classification is mandatory for the clinician to provide prompt and appropriate management of this life-threatening complication.

Disclosure of Interest: None declared

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SLE, Sjögren's and APS – treatment

FRI0303 EFFICACY AND SAFETY OF USTEKINUMAB IN PATIENTS WITH ACTIVE SYSTEMIC LUPUS ERYTHEMATOSUS: RESULTS OF A PHASE 2, RANDOMISED PLACEBO-CONTROLLED STUDY

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Background: IL12 and IL23 have been linked to SLE pathogenesis.
Objectives: The anti-IL12/23 monoclonal antibody ustekinumab (UST) was evaluated in pts with active SLE.
Methods: We conducted a Ph2, PBO-controlled study in 102 pts with active SLE. Pts were randomised(3:2) to UST IV~6 mg/kg or PBO at wk0, followed by UST SC 90 mg or PBO injections q8w, both added to standard care. Primary endpoint was proportion of pts achieving SLE responder index(SRI)−4 response at wk24. Secondary endpoints were change from baseline(BL) in SLEDAI-2K, PGA and BICLA response. Additional pre-specified endpoint analyses included no BILAG worsening(defined as no new BILAG A and ≤1 new BILAG B) and BILAG flare (≥1 new BILAG A or ≥2 new BILAG B).
Results: SRI-4 response occurred in 60% UST vs 31% PBO pts(p=0.005) at wk24 (table 1). UST pts had greater median change from BL in SLEDAI-2K and PGA vs PBO. No difference was observed in BICLA response at wk24; however, in the UST group vs PBO, more pts had no BILAG worsening, and the risk of a new BILAG flare was significantly lower(HR 0.11 [95% CI 0.01–0.94];p=0.0078). UST demonstrated improvement in musculoskeletal and mucocutaneous disease features vs PBO (table 1). Through wk24, 78% UST vs 67% PBO pts had ≥1 AE; 8.3%–9.5%, respectively, had ≥1 SAE; there were no deaths. The overall safety profile was comparable between UST and PBO.

Abstract FRI0303 – Table 1. Efficacy Results at Wk 24.

	PBO	UST
Pts randomised, n	42	60
SRI-4 response, n (%)	13 (31.0)	36 (60.0)
P value		0.005[a]
Change from baseline SLEDAI-2K, median (range)	−2.0 (-20; 10)	−6.0 (-10; 3)
P value		0.026[a,b]
Change from baseline PGA, median (range)	−1.6 (-5.6; 2.7)	−2.5 (-6.6; 2.8)
P value		0.211[a,b]
BICLA response, n (%)	14 (33.3)	21 (35.0)
P value		0.994[a]
Pts with no BILAG worsening, n/N (%)	11 (26.2)	29 (48.3)
P value		0.028
Pts with≥50% improvement from baseline in joint activity[c],% (95% CI)	63.2 (61.7–64.6)	87.7 (86.8–88.6)
P value		0.021[d]
Pts with≥50% improvement from baseline in CLASI activity score[d],% (95% CI)	25.2 (23.1–27.4)	58.7 (57.4–60.1)
P value		0.043[e]

[a]Prespecified analyses; all other analyses were post-hoc.
[b]One-sided test for no difference between treatment groups using a Wilcoxon non-parametric median test for difference of location
[c]Pt subpopulation (67% of total) with ≥4 active joints at baseline
[d]Pt subpopulation (58% of total) with baseline CLASI activity score ≥4
[e]Proportion of responders and p values based on mITT analysis using a multiple imputation model for missing data from wks 16 to 24
BICLA, BILAG-based Combined Lupus Assessment; BILAG, British Isles Lupus Assessment Group; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; SLEDAI-2K, ;Systemic Lupus Erythematosus Disease Activity Index 2000 PGA, physician's global assessment

Conclusions: UST treatment showed efficacy in pts with active SLE and was well-tolerated. UST may work via a novel mechanism of action in SLE.

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FRI0304 LONG-TERM AND LOW-DOSE IL-2 THERAPY MAINTAINS THE TH17/TREG BALANCE IN PERIPHERAL BLOOD OF PATIENTS WITH PRIMARY SJÖGREN'S SYNDROME

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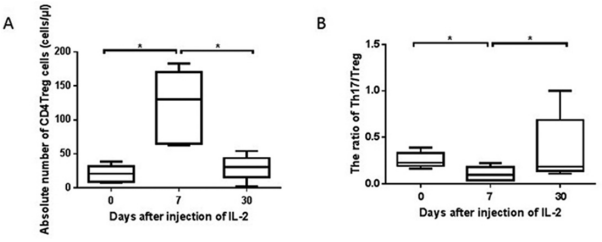
Background: Primary Sjögren's syndrome (pSS) is a chronic autoimmune disease mainly affecting exocrine glands. To date, evidence-based guidelines for the management of pSS are lacking. Regulatory T cells (Tregs) are crucial in maintaining immune tolerance and immune homeostasis, but their role in pSS is unclear. Furthermore, low–dose Interleukin-2 (IL-2) has been shown considerable curative effect on expansion of (Tregs) in patients with GVHD. However, the effects of low-dose IL-2 on Tregs and Th17 cells in pSS are not fully elucidated.
Objectives: To explore the long-term effects of low dose IL-2 on Treg cells, Th17 cells and the ratio of them in peripheral blood of Chinese Han patients with primary SjÖgren's syndrome.
Methods: A total of 190 pSS patients consented at enrollment to donate PB samples for comprehensive immune-phenotyping. In the study, BD Trucount tubes with the lyophilized pellet of a known number of internal counting beads were used for determining absolute counts of total $CD4^+$ T cells in PB and then calculating the absolute number of Th17 cells and $CD4^+$Tregs. Eighty eight in 190 were given low-dose recombination human IL-2 (rhIL-2,50 WIU/day for 5 days and then 50WIU/w for several months) by hypodermic injection combined with standard therapy, which includes glucocorticoid, immune-suppressants, biological agents or combination of them, while others (12 in 69) were given standard therapy only.
Results: ([1]The absolute number of Treg cells decreased significantly in peripheral blood of pSS patients compared with that of healthy control.[2]After short period therapy of low dose rhIL-2, Treg cells increased rapidly in one week but decreased to a lower level after one month[20.91 (9, 31.75) vs. 130.31 (65.18, 170.12) vs. 30.37(,[16, 44] p<0.01]. At the same time the ratio of Th17/Treg cells decreased rapidly in one week but increased to a higher level after one month[0.23 (0.19, 0.33) vs. 0.09 (0.04, 0.18) vs. 0.18 (0.14, 0.69), p<0.1].[3]Long-term IL-2 could maintain the higher level of CD4Treg cells and the balance of Th17/Treg.[4]Patients with balanced Th17/Treg have more obvious improvement of symptoms and more significantly decreased dose of glucocorticoid and HCQ compared with standard therapy group.



Abstract FRI0304 – Figure 1. The change of absolute numbers of Treg cells (A) and the ratio of Th17/Treg (B) after short-term and low-dose IL-2 therapy. (A) Absolute number (cells/μl) of Treg cells increased rapidly 7 days after IL-2 therapy but decreased to a lower level after 30 days. (B) Ratio of Treg cells decreased rapidly 7 days after IL-2 therapy but increased to a higher level after 30 days. Data are presented as median (Q1, Q3). Statistical analysis was performed using the Related Samples Firedman's Two-Way Analysis of Variance by Ranks. * P<0.05, ** P < 0.01, *** P < 0.001 vs. Healthy controls. Asymptotic significances (2-sided tests) are displayed. The significance level is p<0.05.

Conclusions: Therapy of low dose rhIL-2 could promote the proliferation of Treg cells and rebuild the balance of Th17/Treg for both short and long term. To rebuild

the balance of Th17/Treg for long-term, we should use IL-2 for a long time. Balance of Th17/Treg cells in pSS patients predicts a good prognosis.

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FRI0305 PHASE 2 TRIAL OF INDUCTION THERAPY WITH ANTI-CD20 (RITUXIMAB) FOLLOWED BY MAINTENANCE THERAPY WITH ANTI-BAFF (BELIMUMAB) IN PATIENTS WITH ACTIVE LUPUS NEPHRITIS

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Background: Despite case series suggesting efficacy, controlled trials of anti-CD20 in lupus nephritis (LN) did not confirm benefit;*Arthritis Rheum* 2012 64:1215 and 2013;65:2368).
Objectives: One possible explanation for this failure stems from the fact that B cell depletion stimulates production of B cell activating factor (BAFF) which, in turn, facilitates maturation of autoreactive B cells in lymphoid organs or during B cell repopulation. The CALIBRATE study (NCT 02260934) was designed to test this hypothesis, to determine whether addition of anti-BAFF could enhance the clinical effects of anti-CD20, and to assess safety of the combination.
Methods: Forty-three patients with active LN despite conventional treatment enrolled in a prospective randomised open-label trial that compared two treatment strategies. All subjects received iv rituximab (1000 mg), CTX (750 mg), and methylprednisolone (100 mg) at wks 0 and 2, followed by 40 mg/d prednisone tapered to 10 mg/d by wk 12. At wk 4, subjects received either belimumab (10 mg/kg iv at wks 4, 6, 8 and then every 4 wks) plus prednisone (n=21) or prednisone alone (n=22). Complete response (CR) was defined as: (i) urine protein:creatinine ratio (UPCR) <0.5; (ii) eGFR $\geq$120 or, if <120, eGFR >80% of screening; and (iii) prednisone tapered to 10 mg/d. The definiton of partial response (PR) differed only in the UPCR criterion (>50% reduction).
Results: The clinical outcome at wk 24 was similar in both groups (table 1). The CR rate was 24% in the belimumab group (RCB) and 23% in the control group (RC). Three subjects in each group withdrew (WD) prior to wk 24 (two withdrawals in each group due either to progressive nephritis or an infusion reaction, and one in each group for reasons unrelated to SLE or its treatment). B cell depletion from blood was virtually absolute in both groups at wk 12, but the pace of recovery differed. Six subjects experienced serious adverse events between wks 0 and 24; three subjects in the RC group (pneumonia followed by LN flare; deep vein thrombosis; SLE flare); and three subjects in the RCB group (anti-CD20 infusion reaction; soft-tissue abscesses prior to anti-BAFF treatment; quadriceps tendon rupture).
Median B Cell Count Median IgG Level
CR PR NR WD Wk 0 Wk 12 Wk 24 Wk 0 Wk 24
RC Group 23%–23% 41%–14% 105 1 31 1050 1100
RCB Group 24% 24% 38% 14% 143 1 3 984 837:
Conclusions: An interim analysis of data from CALIBRATE shows: (i) anti-BAFF following anti-CD20 for LN did not improve clinical outcome at week 24; (ii) anti-BAFF delayed blood B cell reconstitution following B cell depletion; and (iii) anti-BAFF following anti-CD20 was not associated with hypogammaglobulinemia or an increase in serious infections. Further analyses at 48 weeks and beyond will address how anti-BAFF therapy affects quantitative and qualitative recovery of B cells as well as long-term clinical outcome.
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FRI0306 DEVELOPMENT OF BAFF AND ICOSL BISPECIFIC INHIBITOR AMG 570 FOR SLE TREATMENT

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Background: Systemic lupus erythematous (SLE) is a heterogeneous disease lacking highly effective treatment options. Among many cell types and pathways involved in SLE pathogenesis, aberrant B cells and T cells are critical drivers in autoantibody production and tissue damage. Autoreactive T cells drive autoreactive B cell expansion and autoantibody production. Amongst key pathways that modulate the function of these cells, inducible costimulator ligand (ICOSL) is critical for T follicular helper cell (T_{FH}) development and T memory cell homeostasis, while B cell activating factor (BAFF) is a critical B cell survival factor. We hypothesised that targeting both BAFF and ICOSL would be more efficacious than single BAFF or ICOSL inhibition in SLE and other autoimmune diseases.
Objectives: We tested if targeting both BAFF and ICOSL has superior efficacy than single target inhibition in the mouse arthritis and lupus models. We aimed at generating BAFF and ICOSL bispecific molecule for potential treatment of autoimmune diseases such as SLE.
Methods: Murine BAFF/ICOSL bispecific, combination of BAFF and ICOSL inhibitors or single inhibitor was evaluated in the sheep red blood cell (SRBC) challenge model, mouse collagen induced arthritis (CIA) model, or NZB/NZW lupus models. AMG 570 was tested for human and cyno BAFF and ICOSL binding affinities by Kinexa A. AMG 570 dual target blocking activities was evaluated in human and cyno BAFF and ICOSL mediated B cell and T cell assay, respectively. Pharmacodynamics effect of AMG 570 was evaluated in cynomolgus monkey
Results: Compared to treatment with single inhibitor, combination of BAFF and ICOSL inhibitors was more effective in aemliorating arthritis incidence and severity in the mouse CIA model and NZB/NZW lupus model. The murine BAFF/ICOSL bispecific molecule inhibited murine BAFF and ICOSL mediated B and T cell bioassays, and dual target inhibition in mice. In addition, treatment with murine BAFF/ICOSL bispecific was more efficacious than single BAFF and ICOSL inhibitor in reducing anti-dsDNA IgG, delaying the onset of protenuria and improving survival in the NZB/NZW lupus model. AMG 570 was selected as the clinical candidate with high binding affinity for human BAFF and ICOSL and strong potency in the human B cell and T cell bioassays. B cell reduction was observed after AMG 570 treatment in cynomolgus monkey, consistent with the pharmacological effect of BAFF inhibition.
Conclusions: Inhibition of both BAFF and ICOSL is more efficacious than single target inhibition in the mouse lupus and arthritis models. By targeting both BAFF and ICOSL, AMG 570 has the potential to achieve a large treatment effect size in autoimmune diseases such as SLE and rheumatoid arthritis.
Disclosure of Interest: H. Hsu Shareholder of: Amgen, M. Zhang Shareholder of: Amgen, K. Miner Shareholder of: Amgen, G. Kevin Shareholder of: Amgen, J. Whoriskey Shareholder of: Amgen, R. Jacobsen Shareholder of: Amgen, C. Chen Shareholder of: Amgen, K. Ishida Shareholder of: Amgen
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FRI0307 TBK1 INHIBITION DOWNREGULATES EXPRESSION OF INTERFERON TYPE I AND THE UPREGULATED EXPRESSION OF RIG-LIKE RECEPTORS AND DNA-SENSING RECEPTORS IN INTERFERON POSITIVE PRIMARY SJÖGREN'S SYNDROME PATIENTS

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Background: Type I interferon (IFN-I) upregulation is a hallmark of systemic autoimmune diseases like primary Sjögren's syndrome (pSS). Expression of IFN-I is induced by three different receptor families: Toll-like receptors (TLRs), RIG-like receptors (RLRs) and DNA-sensing receptors (DSRs). Previously we have shown increased mRNA levels of TLRs and RLRs in plasmacytoid dendritic cells (pDC) and CD14 +monocytes of IFN-I positive (IFNpos) pSS patients.[1] TANK-binding kinase (TBK1), is an important signalling hub downstream of RLRs and DSRs and leads to production of IFN-I and subsequent induction of interferon-stimulated genes (ISGs).
Objectives: Study RLRs and DSRs in pSS and explore the potential of a TBK1 inhibitor to downregulate IFN-I activation.
Methods: Expression of RLRs and DSRs was assessed by RQ-PCR and flowcytometry in CD14 +monocytes, BDCA4 +CD123+pDC and CD19 +B cells from IFNpos pSS patients. pDCs from IFNpos pSS patients were analysed by flowcytometry for phosphorylated-TBK1 (pTBK1). PBMCs of pSS patients were cultured with a TBK1 inhibitor, BX795, followed by analysis of IFN-I production and expression of ISGs.