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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Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2018-eular.2337

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 ≥120 or, if <120, eGFR >80% of screening; and (iii) prednisone tapered to 10 mg/d. The definition 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.

Acknowledgements: Conducted by ITN with support from NIAID (UM1AI109565) and Genentech.

Disclosure of Interest: C. Aranow Grant/research support from: GlaxoSmithKline, Consultant for: GlaxoSmithKline, M. Dall'Era Consultant for: Genentech, M. Byron: None declared, L. Ding: None declared, D. Smilek: None declared, B. Diamond: None declared, D. Wofsy Consultant for: GlaxoSmithKline, Celgene, Novartis, UCB, Sanofi

DOI: 10.1136/annrheumdis-2018-eular.5711

FRI0306

DEVELOPMENT OF BAFF AND ICOSL BISPECIFIC INHIBITOR AMG 570 FOR SLE TREATMENT

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Background: Systemic lupus erythematosus (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 ameliorating 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 proteinuria 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

DOI: 10.1136/annrheumdis-2018-eular.5767

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.

Results: In addition to upregulated mRNA levels of RLRs IFIH1 (encoding for MDA5) and DDX58 (encoding for RIG-I), which we previously observed in pDC and monocytes of IFNpos pSS patients, gene expression of IFIH1 and DDX58 was also upregulated in B cells. Upregulation of mRNA levels of the DSRs IFI16 and ZBP1 was observed in monocytes and B cells from IFNpos patients. In pDC protein expression of MDA5, ZBP-1, IFI16 was increased in IFNpos pSS, while there were no differences in RIG-I. In monocytes protein expression of MDA5 was increased and a trend was visible for RIG-I and IFI16. B cells showed increased protein expression of MDA5 and a trend was observed for RIG-I, ZBP-1 and IFI16. These data indicate upregulation of RLRs and DSRs particularly in pDC of IFNpos pSS patients. To further look into the signalling of RLRs and DSRs, phosphorylation of TBK was studied in pDC, the main IFN-I producers, of pSS patients. Increased expression of pTBK1 was observed in pDCs from IFNpos pSS. Upon treatment with BX795, PBMCs from IFNpos pSS downregulated the production of IFN-I and mRNA expression of the ISGs MxA, IFI44, IFI44L, IFIT1 and IFIT3.

Conclusions: RLRs and DSRs are upregulated in IFNpos pSS. Signalling of these receptors could be blocked using a TBK1 inhibitor, which reduced IFN-I protein production and expression of ISGs in PBMCs of IFNpos pSS patients. As patented pharmacological inhibitors, amongst others a small molecule inhibitor, are available TBK1 inhibition is indicated as a potential future treatment target for IFNpos pSS.

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Acknowledgements: The research for this manuscript was (partly) performed within the framework of the Erasmus Postgraduate School Molecular Medicine. The authors thank patients and healthy volunteers for taking part in this study.

Disclosure of Interest: I. Bodewes: None declared, E. Huijser: None declared, C. van Helden-Meeuwse: None declared, L. Tas: None declared, R. Huizinga: None declared, V. Dalm: None declared, M. van Hagen: None declared, N. Groot: None declared, S. Kamphuis: None declared, P. van Daele: None declared, M. Versnel Grant/research support from: Research funding Domainex

DOI: 10.1136/annrheumdis-2018-eular.4641

FRI0308

CORTICOSTEROIDS COMBINED WITH DOUBLET OR SINGLE-AGENT IMMUNOSUPPRESSIVE THERAPY FOR ACTIVE PROLIFERATIVE LUPUS NEPHRITIS

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Background: Current evidence exploring whether corticosteroids (C) plus doublet immunosuppressive therapy (IT) is superior to the classical combination of C with single-agent IT for active proliferative lupus nephritis (LN) is controversial.

Objectives: We aimed to clarify the efficacy and safety of C+doublet versus single-agent IT for active proliferative LN by a meta-analysis.

Methods: We searched for randomised clinical trials that evaluated the benefits and risks of C+doublet versus single-agent IT for active proliferative LN. The primary outcome was overall response rate (ORR). The second outcomes were the change from baseline in Systemic Lupus Erythematosus Disease Activity Index (SLE-DAI) score, negative conversion ratio of anti-double-stranded DNA (anti-dsDNA), and adverse events. The quality of the evidence was evaluated with the GRADE framework. The PROSPERO registry number is CRD42017068491.

Results: The analysis included 10 trials with 1587 unique patients. Compared with C+single agent IT, C+doublet IT was statistically significant with higher ORR (relative risk [RR], 1.22; 95% confidence interval [CI], 1.09 to 1.35; $p < 0.0001$; moderate certainty). In subgroup analysis, C+doublet IT without biologics resulted into significant higher ORR than C+single agent IT (RR, 1.30; 95% CI, 1.13 to 1.50; $p < 0.0001$; moderate certainty), while C+doublet IT including biologics improved ORR only for refractory severe LN (RR, 1.46; 95% CI, 1.09 to 1.96; $p = 0.012$; very-low certainty). A larger change from baseline in SLE-DAI score (standardised mean difference, -0.49 ; 95% CI, -0.68 to -0.30 ; $p < 0.0001$; moderate certainty) and a higher negative conversion ratio of anti-dsDNA (RR, 1.34; 95% CI, 1.06 to 1.69; $p = 0.014$; high certainty) were observed with C+doublet IT than with C+single agent IT. The rates of adverse events were similar between the two regimens (high to moderate certainty).

Conclusions: Compared with single-agent IT, the combination of corticosteroids with doublet IT improved clinical outcomes for active proliferative LN. C+doublet

IT including biologics may be a better regimen for refractory severe LN. There is imperative that prospective biomarker-driven trials to identify patients for whom C+doublet IT is most efficacious.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2018-eular.1950

FRI0309

THE IMPACT OF BELIMUMAB AND RITUXIMAB ON HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Background: Accumulating evidence supports an impaired health-related quality of life (HRQoL) in patients with systemic lupus erythematosus (SLE). The impact of modern therapeutic interventions on patients' perception of HRQoL has not been explored in depth.

Objectives: The aim of this study was to investigate the effects of two biologic treatments – belimumab and rituximab – on SLE patients' HRQoL, fatigue and functional ability.

Methods: Patients with SLE from the Karolinska University Hospital treated with either belimumab (n=34) or rituximab (n=35) were included. Data were collected prospectively at treatment initiation and at months 3, 6, 12 and 24; these included the Medical Outcome Study short form-36 (SF-36) version 2, functional assessment of chronic illness therapy (FACIT)-Fatigue scale version 4, EuroQol research foundation 5-dimension (EQ-5D) health questionnaire, and Stanford health assessment questionnaire disability index (HAQ-DI).

Results: Substantial reductions compared to Swedish norms were observed across all SF-36 subscales at baseline (figure 1). SF-36 mental component summary scores were higher in patients who were on antimalarial agents (mean: 42.7; SD ± 11.8 ; n=29) compared to patients who were not (mean: 34.0; SD ± 14.7 ; n=32; $p = 0.019$). Accordingly, patients who were on antimalarial agents performed better in SF-36 social functioning (mean: 63.7 versus 46.5; $p = 0.022$) and mental health (mean: 68.7 versus 53.4; $p = 0.023$) compared to patients who were not. Belimumab-treated patients reported gradual improvements in the SF-36 physical summary component (significant from month 12; $p = 0.023$) and FACIT-Fatigue (significant by month 24; $p = 0.001$), no changes in EQ-5D scores, and improvements in HAQ-DI by month 6 ($p = 0.014$). Rituximab-treated patients reported rapid improvements in the SF-36 mental summary component and FACIT-Fatigue by month 3 ($p = 0.031$ and $p = 0.007$, respectively), which declined at month 12, as well as improvements in EQ-5D at month 6 ($p = 0.016$) and HAQ-DI at month 3 ($p = 0.033$), which were not maintained at later time points.

Conclusions: HRQoL was considerably impaired in SLE patients compared to population-based norms at baseline, and was not fully compensated during follow-up. Patients' perceptions of HRQoL showed treatment-specific patterns over time, and could prove useful when evaluating the effects of biologics in SLE. Early evaluation of belimumab might underestimate improvements in HRQoL and fatigue. In severe SLE, antimalarial agents may have favourable effects on mental HRQoL aspects.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2018-eular.3006