OP0204 **IMPACT OF ANTI-DRUG ANTIBODY AND INJECTION SITE REACTION ON EFFICACY: 24-WEEK RESULTS FROM A PHASE III STUDY COMPARING SB4 (ETANERCEPT BIOSIMILAR) WITH REFERENCE ETANERCEPT IN PATIENTS WITH RHEUMATOID ARTHRITIS**

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Background: SB4 is approved by the European Commission as a biosimilar of the reference etanercept (ETN). The phase III clinical study results have been reported previously.[1,2] Data to date shows no correlation between the development of anti-drug antibody (ADA) and clinical response or adverse events with etanercept treatment.
Objectives: To investigate the impact of the presence of ADA or injection site reaction (ISR) on efficacy in patients with rheumatoid arthritis (RA) treated with SB4 or ETN up to week 24.
Methods: In this phase III randomised, double blind study, patients with moderate to severe RA received 50 mg/week of either SB4 or ETN with background methotrexate (MTX) for 52 weeks. Efficacy, safety and immunogenicity were assessed.
Results: Up to week 24, the incidence of ADA (2 patients [0.4%] in SB4 vs 39 patients [13.1%] in ETN, $p < 0.001$) and the incidence of ISR (9 patients [3.0%] in SB4 vs 48 patients [16.2%] in ETN, $p < 0.001$) were significantly lower in SB4 compared to ETN. Due to the low incidence of ADA in the SB4 treatment group, the impact of ADA on efficacy could not be evaluated. Within the ETN treatment group at week 24, there was a trend towards increased efficacy (ACR20, ACR-N, change in DAS28, remission and low disease activity based on DAS28, SDAI, or CDAI) in patients without detectable ADA compared to patients with ADA (Table). In regards to ISR, efficacy tended to be higher in patients who did not experience ISR compared to those who did within each treatment group.
There was no correlation between the presence of ADA and incidence of ISR. In patients without detectable ADA and patients with ADA, respectively, 3.0% (9/297) vs. 0.0% (0/2) of patients from SB4 group and 16.3% (42/248) vs. 15.4% (6/39) of patients from the ETN group experienced ISR.

Table. Efficacy at week 24 by presence of ADA and ISR

	SB4 50 mg		ETN 50 mg	
	(+) ADA (n=2)	(−) ADA (n=297)	(+) ADA (n=39)	(−) ADA (n=257)
ACR20	2/2 (100.0%)	218/285 (76.5%)	24/36 (66.7%)	189/236 (80.1%)
ACR50	1/2 (50.0%)	127/285 (44.6%)	15/36 (41.7%)	101/236 (42.8%)
ACR70	0/2 (0.0%)	69/285 (24.2%)	9/36 (25.0%)	50/236 (21.2%)
ACR-N	48.8±19.38	45.0±29.14	40.3±30.33	44.3±27.70
Change in DAS28	−2.98±1.063	−2.57±1.375	−2.09±1.407	−2.57±1.295
Change in SDAI	−33.50±3.394	−25.69±14.641	−23.78±15.230	−25.37±12.831
Change in CDAI	−32.65±4.596	−24.73±14.120	−22.45±14.396	−24.57±12.750
	(+) ISR (n=9)	(−) ISR (n=290)	(+) ISR (n=48)	(−) ISR (n=249)
ACR20	5/7 (71.4%)	215/280 (76.8%)	30/39 (76.9%)	183/233 (78.5%)
ACR50	1/7 (14.3%)	127/280 (45.4%)	14/39 (35.9%)	102/233 (43.8%)
ACR70	1/7 (14.3%)	68/280 (24.3%)	7/39 (17.9%)	52/233 (22.3%)
ACR-N	32.6±28.18	45.3±29.06	41.8±28.80	44.1±27.95
Change in DAS28	−1.81±1.282	−2.59±1.371	−2.31±1.280	−2.54±1.324
Change in SDAI	−20.55±11.986	−25.86±14.654	−21.56±12.233	−25.77±13.216
Change in CDAI	−20.17±11.462	−24.88±14.140	−20.74±12.062	−24.89±13.036

Data are presented in either n' (%) or mean ± standard deviation.
ACR20/50/70: American College of Rheumatology 20%/50%/70% response rate; ACR-N: numeric index of the ACR response; ADA: anti-drug antibody; CDAI: clinical disease activity index; DAS28: disease activity score measured by 28 joints; ISR: injection site reaction; LDA: low disease activity; SDAI: simplified disease activity index.
ADA and ISR status defined positive for patients with at least one ADA or ISR up to week 24 regardless of the result at week 0.
ISR counted by treatment-emergent adverse event with high-level group term of administration site reactions.

Conclusions: Significantly fewer patients from SB4 developed ADA or experienced ISR compared to ETN, however the efficacy was still comparable between SB4 and ETN in patients without detectable ADA and in patients who did not experience ISR. Within the ETN group, there was a trend towards increased efficacy in patients without detectable ADA compared to patients with ADA. In both SB4 and ETN group, patients with ISR tended to have higher efficacy than patients without ISR. There was no correlation between the presence of ADA and ISR.

References:
[1] Emery P et al. Ann Rheum Dis. 2015 Jul 07.
[2] Vencovsky J et al. Arthritis Rheumatol. 2015; 67 (suppl 10).

Disclosure of Interest: J. Vencovsky Consultant for: Samsung Bioepis Co., Ltd., Biogen, P. Emery Grant/research support from: Abbvie, BMS, Pifzer, USB, MSD, Novartis, Lilly, Consultant for: Samsung Bioepis Co., Ltd., E. Keystone Grant/research support from: Abbott, Amgen, AstraZeneca, BMS, Janssen, Lilly, Novartis, Pfizer, Consultant for: Abbott, AstraZeneca, Biotest, BMS, Genentech, Janssen, Lilly, Merck, Pfizer, Samsung Bioepis, Speakers bureau: Abbott, AstraZeneca, BMS Canada, Janssen, J. Ghil Employee of: Samsung Bioepis Co., Ltd., S. Y. Cheong Employee of: Samsung Bioepis Co., Ltd., E. Hong Employee of: Samsung Bioepis Co., Ltd.
DOI: 10.1136/annrheumdis-2017-eular.3043

THURSDAY, 15 JUNE 2017

Which target / outcome is more relevant in the management of SLE?

OP0205 **ASSOCIATION BETWEEN T FOLLICULAR HELPER CELL AND PLASMABLAST CORRELATES WITH DISEASE ACTIVITY IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS**

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Background: Various immunological abnormalities contribute to the development and perpetuation of systemic lupus erythematosus (SLE). Since SLE is a molecularly heterogeneous disease, targeted therapy has not yet been fully established. It seems to be important to explore the characteristic and interaction among the immune cell phenotypes in this disease.
Objectives: The aim of this study was to assess the relationship between the peripheral immune cell phenotypes with clinical manifestations and responsiveness to immunosuppressive therapy in patients with SLE.
Methods: Peripheral blood mononuclear cells were obtained from 143 SLE patients and 26 healthy donors (HD). The blood samples were taken at baseline and week 24 after treatment. The subset of circulating B, T and dendritic cells was defined based on comprehensive 8-color flow cytometric analysis for human immune system termed "the Human Immunology Project" proposed by the National Institutes of Health (NIH) and the Federation of Clinical Immunology Societies (FOCIS). The correlation of immune cell phenotypes with clinical characteristics and responsiveness to immunosuppressive therapies, such as cyclophosphamide, mycophenolate mofetil, or calcineurin, in addition to high-dose glucocorticoids, were evaluated. Patients who were required more than two different immunosuppressant therapies in addition to glucocorticoids were considered treatment resistant.
Results: The frequency of $CD3^+CD4^+CXCR5^+ICOS^+$ T follicular helper (Tfh) cell, but not $CD3^+CD4^+CXCR3^+CCR6^-$ Th1 cell and $CD3^+CD4^+CXCR3^-CCR6^+$ Th17 cell, were higher in SLE than that in HD (mean 1.1 vs 0.8, p=0.01). The frequency of $CD19^+CD20^+IgD^+CD27^+$ central memory B cell and $CD19^+CD20^+IgD^-CD27^-$ effector B cell were higher in SLE than that in HD (mean 23.6 vs 15.1 and 10.7 vs 5.2, $p \leq 0.001$ and $p < 0.001$, respectively). The largest difference relative to the HD was observed in the proportion of $CD19^+CD20^-CD27^+CD38^+$ plasmablast, which was higher in SLE (mean 16.2 vs 3.7, $p < 0001$) and correlated with BILAG index ($r=0.24$, $p < 0.001$). The proportion of Tfh cell significantly correlated with serum IgG level ($r=0.35$, $p < 0.001$), and the proportion of $CD3^+CD4^+CXCR5^+ICOS^+CD69^+$ activated Tfh cell correlated with serum anti-Sm antibody level ($r=0.26$, p=0.01). Among helper T cell subsets (Th1, Th17, Treg and Tfh), the proportion of Tfh cell only showed positive correlation with that of plasmablast ($r=0.24$, p=0.02). Treatment resulted in marked improvement in disease activity scores, such as SLEDAI and BILAG and resulted in significant decreased proportions of plasmablast and Tfh cell (plasmablast; mean 17.6 to 10.1, $p < 0.01$, Tfh; mean 1.1 to 0.7, $p < 0.01$). The percentage of patients who showed treatment resistance was highest among patients with high percentage of Tfh cell (p=0.03).
Conclusions: Peripheral immuno-phenotyping confirmed the importance of Tfh cell and plasmablast in patients with SLE, *i.e.* activation of Tfh cell correlated with autoantibody production while plasmablast did with disease activity of SLE. Our findings supported the relevance of Tfh cell-plasmablast axis as a potential therapeutic target for SLE. The peripheral immunophenotyping might be useful in evaluating the pathogenesis and in determining the therapeutic target of each patient.
Disclosure of Interest: S. Nakayamada: None declared, S. Kubo Speakers bureau: Bristol-Myers, M. Yoshikawa: None declared, Y. Miyazaki: None declared, S. Iwata: None declared, I. Miyagawa: None declared, K. Nakano: None declared, K. Saito: None declared, Y. Tanaka Grant/research support from: Mitsubishi-Tanabe, Takeda, Daiichi-Sankyo, Chugai, Bristol-Myers, MSD, Astellas, Abbvie, Eisai, Speakers bureau: Abbvie, Chugai, Daiichi-Sankyo, Bristol-Myers, Mitsubishi-Tanabe, Astellas, Takeda, Pfizer, Teijin, Asahi-kasei, YL Biologics, Sanofi, Janssen, Eli Lilly, GlaxoSmithKline
DOI: 10.1136/annrheumdis-2017-eular.4165

OP0206 **PERFORMANCE OF SLEDAI-2K TO DETECT A CLINICALLY MEANINGFUL CHANGE IN SLE DISEASE ACTIVITY: A 36-MONTH PROSPECTIVE COHORT STUDY OF 334 PATIENTS**

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Background: The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) is the core determinant of response in the SLE Responder Index (SRI), a primary efficacy outcome in SLE clinical trials. However, SLEDAI is unable to discriminate partial improvement/worsening, as it scores each item

categorically. Furthermore, potentially severe lupus manifestations, such as hemolytic anemia are not scored in SLEDAI.
Objectives: To evaluate the performance of SLEDAI-2K to detect a clinically meaningful change in SLE disease activity.
Methods: Prospective cohort study of SLE patients followed at a tertiary care lupus clinic from January 2014 to December 2016. Consecutive patients fulfilling the ACR'97 and/or the SLICC'12 classification criteria were included. At each outpatient visit, disease activity from the last 30 days was scored in the Physician Global Assessment (PGA) (0–3 cm scale) and in SLEDAI-2k. The association between PGA and SLEDAI-2K at each visit was tested with Spearman's Correlation. A clinically meaningful change in SLE disease activity was defined as difference in PGA $\geq$0.3 cm at follow-up compared to the baseline visit. Performance of change in SLEDAI-2K was tested in two models: against worsening and improvement in PGA $\geq$0.3 cm from baseline using Receiver Operating Characteristic (ROC) curve analysis. Sensitivity, specificity, positive and negative predictive values (PPV, NPV) of SLEDAI-2k to change in PGA was calculated. Statistical significance was set at 0.05.
Results: We included 334 patients (87.1% female, mean age at baseline - 44.8±14.5 years). At baseline, median PGA and SLEDAI-2k score was 0.2 points (range 0–2.5) and 2 points (range 0–19), respectively. Eighty-three patients (24.8%) had a PGA $\geq$0.4 points at baseline. During follow-up of 36 months, 2129 visits were performed. PGA and SLEDAI-2K scores presented a high correlation (rho=0.82, $p<0.0001$) (fig. 1). Reductions in SLEDAI-2K presented in ROC analysis an area under curve (AUC) of 0.697 [95% CI (0.628–0.766), $p<0.0001$] for an improvement in PGA$\geq$0.3. For a worsening of PGA$\geq$0.3 points, increase in SLEDAI-2K presented an AUC of 0.877 [95% CI (0.822–0.932), $p<0.0001$]. Estimated sensitivities, specificities, PPV and NPV are presented in table 1.

Table 1. Performance of Sledai-2K to detect a clinically meaningful change in PGA, using cut-offs of decrease and increase (for a clinical improvement and worsening, respectively) in SLEDAI-2K $\geq$1 and $\geq$4 points

	Δ SLEDAI-2K≥1				Δ SLEDAI-2K≥4			
	Sens.	Spec.	PPV	NPV	Sens.	Spec.	PPV	NPV
Improvement PGA≥0.3	0.7	0.571	0.397	0.825	0.288	0.929	0.622	0.763
Worsening PGA≥0.3	0.725	0.903	0.627	0.936	0.353	0.996	0.947	0.873

Sens: Sensitivity; Spec: Specificity; PPV: Positive predictive value; NPV: Non predictive value.

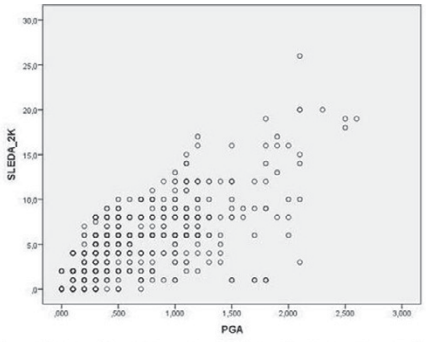

Fig. 1 Scatter diagram showing linear positive correlation between PGA and SLEDAI-2K scores (Spearman's correlation coefficient (rho) = 0.82, p <0.0001).

Conclusions: SLEDAI-2K presents a limited performance in detecting a clinically meaningful change in SLE disease activity, failing to identify more than a quarter of cases with clinically meaningful improvement or worsening. There is a need to optimize SLE disease activity measures.
Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2017-eular.3895

THURSDAY, 15 JUNE 2017

Joint EULAR - EFIS session: tilting the balance: from disease to tolerance induction

OP0207 B CELL DEPLETION INCREASES REGULATORY T CELLS AND AMELIORATES SKIN AND LUNG FIBROSIS IN A BLEOMYCIN-INDUCED SYSTEMIC SCLEROSIS MODEL MOUSE

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Background: B cells play a critical role in systemic autoimmunity and disease expression through various functions such as cytokine production and induction of other immune cell activation. Recently, some clinical studies have shown that the efficacy of B cell depletion therapy with rituximab, a chimeric monoclonal antibody against human CD20, in systemic sclerosis (SSc) patients. However, it still remains unclear why B cell depletion can be an effective treatment for SSc.
Objectives: The purpose of this study is to assess the role of B cell depletion in SSc. We evaluated the skin and lung fibrosis of bleomycin (BLM)-induced SSc model mice treated with B cell depletion. Furthermore, we investigated the effect of B cell depletion on T cell cytokine profile.
Methods: To generate BLM-induced SSc model mice, 300 μg of BLM was injected subcutaneously into the shaved backs of the C57BL/6 mice every other day for 4 weeks. Anti-mouse CD20 monoclonal antibodies, which can deplete mouse B cells, were also injected every 2 weeks from 2 weeks later starting BLM treatment. After 4 weeks of BLM treatment, skin and lung fibrosis were assessed histopathologically. T cells and B cells were isolated from spleen using magnetic cell sorting system. Purified T cells ($5x10^5$ cells) were cultured with B cells ($5x10^5$ cells) in the presence of phorbol 12-myristate 13-acetate, ionomycin, and anti-CD3/CD28 antibodies. Cytokine expressions in the fibrotic skin and lung were quantified by real-time polymerase chain reaction. Cytokine production of T cells and B cells were analyzed by flow cytometric analysis.
Results: Dermal thickness and lung fibrosis score increased in BLM-treated mice compared with phosphate buffer saline (PBS)-treated control mice. Frequencies of interleukin (IL)-10 producing splenic B cells significantly decreased in BLM-treated mice compared with PBS-treated mice, while IL-6 producing B cell frequencies increased. Moreover, interferon (IFN)-γ, IL-4, or IL-17 producing T cell frequencies increased in BLM-treated mice. There were no significant differences in regulatory T cell frequencies between BLM-treated and PBS-treated mice. B cell depletion increased IL-10 producing regulatory T cell frequencies in BLM-treated mice. By contrast, frequencies of IFN-γ, IL-4, or IL-17 producing T cells were significantly decreased by B cell depletion in BLM-treated mice. In addition, fibrogenic cytokine mRNA expression levels of skin and lung decreased in BLM-treated mice with B cell depletion. To assess the role of B cells on T cell cytokine production, purified splenic B cells from BLM- or PBS-treated mice were cultured with naive T cells. T cells which were cultured with B cells from BLM-treated mice produced greater amounts of INF-γ, IL-4, and IL-17 than those cultured with PBS-treated mouse B cells. By contrast, B cells from PBS-treated mice induced a higher amount of IL-10 production from T cells than those from BLM-treated mice.
Conclusions: B cell depletion inhibited skin and lung fibrosis in BLM-treated mice. Furthermore, B cell depletion increased regulatory T cell frequencies in BLM-treated mice, though INF-γ, IL-4, and IL-17 producing T cell frequencies were decreased by B cell depletion. These results suggest that B cell depletion alters T cell cytokine profile, which results in inhibition of fibrosis in this model.
Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2017-eular.4189

OP0208 SYNOVIAL TISSUE OF RA PATIENTS IN REMISSION CONTAINS A UNIQUE POPULATION OF REGULATORY MACROPHAGES

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Background: The majority of RA treatments target inflammation or the adaptive immune response. Partial- or non-response is common and only a minority have sustained remission. There is a knowledge gap in understanding the mechanisms that could reinstate synovial homeostasis in RA. Tissue macrophages may have a role in this process; they are present in healthy synovium and aid resolution of the inflammation in experimental models of RA. However, little is known about the regulatory properties of human synovial tissue macrophages.
Objectives: Our hypothesis is that healthy and RA synovium in remission contain macrophages with anti-inflammatory/repair properties and identifying the effector pathways that drive their function could facilitate therapeutic restoration of synovial homeostasis in RA.
Methods: We developed a flow cytometry sorting strategy for harvesting tissue-resident macrophages obtained from digested synovial biopsies of RA patients (n=21, including in remission n=5; and active RA n=16). Cells were labelled with cell lineage-specific antibodies; then macrophages were gated based on their expression of $CD64^{pos}CD11b^{pos}MHCII^{pos}Lineage^{neg}$. The potential homeostatic/repair macrophage was preliminary identified by the presence of CD206 marker. $CD206^{pos}$ and $CD206^{neg}$ macrophages were sorted using a FACS Aria III and RNAseq performed to characterise their functional signature. In some experiment, macrophages were seeded on collagen-coated plates and production of TNFa evaluated.
Results: All synovial tissue macrophages from RA in remission were $CD206^{pos}$ whereas a substantial number of synovial macrophages from active RA tissue were $CD206^{neg}$. Gene expression analyses and functional assays suggest that these populations represent distinct phenotypes in the activation spectrum. $CD206^{neg}$ macrophages have high expression of microRNA-155, which drives production of inflammatory mediators *e.g.* TNFa. In contrast, $CD206^{pos}$ macrophages showed regulatory properties characterised by increased expression of soluble (*e.g. IL10, TGFB*), surface (*e.g. IL4/14R, TGFBR1/2*) and cellular (*e.g. SHIP1, TAM, SMAD2, STAT6*) inhibitors of inflammatory activation, and increased expression of repair markers (*e.g. ARG2 and CCL18*).
Conclusions: We propose therefore that anti-inflammatory/repair macrophages may be present in human synovial tissues in remission representing a hitherto unnoticed regulatory tissue mechanism.