breakdown of immune self-tolerance, a causative mechanism implicated in multiple autoimmune diseases. Enhanced sensitivity of Tregs to IL-2 supports the use of low-dose IL-2 therapy; however, this treatment is limited by its short half-life and relatively poor selectivity for stimulation of Tregs versus other T cell types. NKTR-358 is a polyethylene glycol (PEG) conjugate of recombinant human IL-2 (aldesleukin sequence with no additional amino acid mutation or substitution). It is differentiated from native IL-2 by its prolonged biological activity as well as its marked and selective stimulation of Tregs in different animal species, including non-human primates.

Objectives: Study objectives assessed the safety and tolerability of NKTR-358 in humans administered single ascending doses subcutaneously (SC). In addition, time course and extent of changes in the numbers and percentages of Tregs, conventional CD4+ and CD8+ T cells, NK cells, cytokine levels, and the pharmacokinetics (PK) of NKTR-358 in peripheral blood were investigated.

Methods: In this first-in-human, double-blind, single ascending dose study, healthy volunteers received SC doses ranging from 0.3 to 28 ug/kg (9 active:3 placebo per cohort) and subjects were followed for 50 days.

Results: All 8 planned cohorts completed dosing. There were no dose-limiting toxicities, serious adverse events, deaths, or clinically significant abnormalities in vital signs, electrocardiograms, or laboratory test values. Adverse events attributed to NKTR-358 were primarily limited to mild (grade 1) injection site reactions. One subject at the highest dose tested demonstrated transient and mild (grade 1) symptoms of elevated cytokine levels and lymphopenia, which resolved without treatment. No other individual at any dose level had systemic signs or symptoms known to be associated with IL-2 therapy. The first 6 cohorts have been tested for anti-drug antibodies to date and none have been detected. NKTR-358 reached maximum plasma levels 4-6 days after administration, with little change for ~2 weeks, and then decreased with a half-life of ~8-9 days. NKTR-358 exhibited linear PK above the 1.0 ug/kg dose.

The primary effect of NKTR 358 was seen on Tregs. In the 3.0 to 28.0 ug/kg dose cohorts, a dose-dependent and sustained increase in the absolute numbers and percentages of circulating CD4+FoxP3+CD25bright Tregs were observed. The elevated levels peaked at Days 10-12 and did not return to baseline until ~20 to 25 days following administration. At 28.0 ug/kg, the mean peak increase in numbers of these CD25bright Tregs was 17-fold above baseline, and the mean peak percentage increased from 0.5% to 7.4%. In addition, there was an increase in Treg activation markers at doses ≥ 13.5 ug/kg. There was a mean increase of 3.5-fold in the percentages and numbers of NK cells at the highest dose tested, but no changes in percentages or numbers of conventional CD4+ or CD8+ T cells were observed. NKTR-358 selectively induced Tregs, evidenced by a 15-fold increase in the mean peak Treg:CD8 ratio over baseline in the 28.0 ug/kg group.

Conclusion: Single doses of the IL-2 conjugate T-reg stimulator, NKTR-358, in the dose range tested were well tolerated and safe. NKTR-358 led to a striking and selective dose-dependent increase in circulating CD25bright Tregs with minimal effects on conventional T cells and with relatively small effects on NK cells. These clinical results extend previous animal studies showing the prolonged and Treg selective action of NKTR-358, and provide strong support for testing NKTR-358 as a new therapeutic in autoimmune diseases, such as systemic lupus.

Disclosure of Interests: Christie Fanton Shareholder of: Nektar Therapeutics, Employee of: Nektar Therapeutics, Suresh Siddhanti Shareholder of: Nektar Therapeutics, Employee of: Nektar Therapeutics, Neha Dixit Shareholder of: Nektar Therapeutics, Employee of: Nektar Therapeutics, Lin Lu Shareholder of: Nektar Therapeutics, Employee of: Nektar Therapeutics, Toufigh Gordi Shareholder of: Nektar Therapeutics, Consultant for: Rosa & Co LLC, Employee of: Nektar Therapeutics, Daniel Dickerson Speakers bureau: Last speaking engagement was 2013, Jonathan Zalevsky Shareholder of: Nektar Therapeutics, Employee of: Nektar Therapeutics, Brian Kotzin Shareholder of: Nektar Therapeutics, Gilead Sciences, Amgen, Rigel Pharmaceuticals, Consultant for: Nektar Therapeutics, Employee of: Nektar Therapeutics

DOI: 10.1136/annrheumdis-2019-eular.3395

OP0196

IMBALANCE BETWEEN MEMORY TH1 AND TH1-TREG CELLS DEPENDS ON DIFFERENTIAL REGULATION OF CELL METABOLISM IN PATIENTS WITH SLE

Shigeru Iwata, Mingzeng Zhang, Maiko Hajime, Naoaki Ohkubo, Hiroko Miyata, Yasuyuki Todoroki, Shingo Nakayamada, Yoshiya Tanaka. *University of Occupational and Environmental Health, Kitakyushu, Japan, Kitakyushu, Japan*

Background: T helper 1 (Th1) cells play an important role in Systemic Lupus Erythematosus (SLE). However, which abnormalities generated in Th1 cells may be related to the pathogenesis of SLE remains elusive. "Immunometabolism" has recently attracted much attention. We previously reported that both IFN- γ and T-bet positively regulated aerobic glycolysis, leading to activation of Th1 cells in mice (REF1). This suggests a potentially important role for metabolic reprogramming in human Th1 cells and the pathogenesis of SLE which requires further investigation.

Objectives: In this study, we assessed the abnormality of metabolism in Th1 cells in patients with SLE. In addition, we investigated which abnormalities of Th1 cells are generated via metabolic reprogramming in vitro.

Methods: Peripheral blood mononuclear cells (PBMCs) were obtained from 31 age-matched healthy donors (HDs) and 60 patients with SLE. Th1- and metabolism-related markers in CD4+ T cells were measured by flow cytometry. In addition, the correlation of these markers with clinical characteristics was investigated. Next, CD4+CD45RA- cells were purified from peripheral of HDs, and the effect of mTORC1 inhibitor Rapamycin (Rapa) or glycolysis inhibitor 2DG on characteristic changes in Th1 cells were assessed in vitro.

Results: Baseline characteristics of patients with SLE were males: females=5:55, age 41.1 years, disease duration 142.3 months, SLEDAI 11.5 and BILAG 12.9 at the timing of admission due to exacerbation of SLE. Activated effector memory CD4+T-bet^{hi} cells in patients with SLE were higher than HDs. The CD4+T-bet^{hi} cells had high potential for IFN- γ production. mTORC1 acts as a regulator of cell growth through the phosphorylation of substrates that potentiate anabolic processes such as aerobic glycolysis. The CD4+T-bet^{hi} cells highly expressed p-mTORC1, and this was closely related to treatment-resistance, but not disease activity and autoantibodies such as anti ds-DNA Abs (Treatment resistance was defined as refractory to >3 kinds of immunosuppressants and/or >2 re-increase to high dose corticosteroid). Therefore, we examined the effect of Rapa or 2DG to such memory mTORC1+T-bet^{hi}IFN- γ CD4+ cells in vitro. When CD45RA-CD4+ cells were isolated from peripheral blood of HDs and stimulated with anti-CD3/CD28 Abs, T-bet expression and IFN- γ production as well as p-mTORC1 expression and glycolysis were induced. Interestingly, 2DG, but not Rapa, suppressed IFN- γ production and, in contrast, enhanced IL-2 production. Therefore, we hypothesized that 2DG induced Th1-Treg cells, reported as one of Treg cell subsets (REF2). 2DG induced FoxP3^{int}T-bet^{hi}IFN- γ (Th1-Treg like) cells and suppressed FoxP3^{int}T-bet^{hi}IFN- γ (Th1 like) cells. Meanwhile, Rapa induced FoxP3^{int}T-bet^{hi}IFN- γ (non-Treg like) cells and did not affect to FoxP3^{int}T-bet^{hi}IFN- γ (Th1 like) cells. Finally, we examined the involvement of Th1-Treg cells to the pathogenesis of SLE. CD45RA- FoxP3^{int}IFN- γ (non-Treg) cells as well as T-bet^{hi} (Th1 like) cells were increased, whereas CD45RA- FoxP3^{int}CXCR3⁺T-bet^{hi} (Th1-Treg) cells were decreased in SLE.

Conclusion: These results indicate that activated effector memory Th1 cells were increased while memory Th1-Treg cells were decreased in patients with SLE. Importantly, metabolic modulators redressing the imbalance of helper T subsets have potential as a new therapeutic strategy.

REFERENCES:

- [1] Iwata S, et al. *Immunity*. 2017;46:983-91.
- [2] Levine AG, et al. *Nature*. 2017;546:421-25.

Disclosure of Interests: Shigeru Iwata: None declared, Mingzeng Zhang: None declared, Maiko Hajime: None declared, Naoaki Ohkubo: None declared, Hiroko Miyata: None declared, Yasuyuki Todoroki: None declared, Shingo Nakayamada Grant/research support from: Mitsubishi-Tanabe, Takeda, Novartis and MSD, Speakers bureau: Bristol-Myers, Sanofi, Abbvie, Eisai, Eli Lilly, Chugai, Asahi-kasei and Pfizer, Yoshiya Tanaka Grant/research support from: Abbvie, Astellas, Bristol-Myers Squibb, Chugai, Daiichi-Sankyo, Eisai, Mitsubishi-Tanabe, MSD, Ono, Taisho-Toyama, Takeda, Speakers bureau: Abbvie, Asahi-kasei, Astellas, Bristol-Myers Squibb, Chugai, Daiichi-Sankyo, Eli Lilly, Eisai, Glaxo-Smithkline, Janssen, Mitsubishi-Tanabe, Novartis, Pfizer Japan Inc, Sanofi, Takeda, UCB, YL Biologics

DOI: 10.1136/annrheumdis-2019-eular.3409

THURSDAY, 13 JUNE 2019

Can imaging improve outcome in OA?

OP0197

EVALUATING THE RELATION OF STRUCTURAL DAMAGE BY MRI TO CLINICAL PAIN SCORES, PAIN SENSITISATION AND TYPE II COLLAGEN DEGRADATION IN KNEE OSTEOARTHRITIS

Nidhi Sofat¹, Vivian Ejindu², Christine Heron², Lena Assi³, Anasuya Kuttapitiya⁴, Guy Whitley⁵, Soraya Koushesh³, Abiola Harrison¹, Franklyn Howe⁶. ¹Infection and Immunity, Musculoskeletal Research Group, London, United Kingdom; ²St George's Hospital, Department of Radiology, London, United Kingdom; ³Institute for Infection and Immunity, Musculoskeletal Research Group, St George's, University of London, London, United Kingdom; ⁴Institute for Infection and Immunity, Musculoskeletal Research Group, St George's, University of London, London, United Kingdom; ⁵Molecular and Clinical Sciences Research Group, St George's, University of London, London, United Kingdom; ⁶Molecular and Clinical Sciences Institute, St George's, University of London, London, United Kingdom

Background: The evolution of pain in relation to damage in the synovium, bone and cartilage in osteoarthritis (OA), coupled with their relation to wet biochemical markers are not well understood.

Objectives: In this study we evaluated the relation between structural damage by MRI, clinical and pain sensitisation measures and wet biochemical biomarkers in knee OA.

Methods: We recruited 130 participants fulfilling ACR criteria with advanced OA requiring total knee replacement (TKR) (n=80), mild OA having standard care (n=42) and non-OA controls (n=8). Knee MRI in 90 subjects (72 F, 18 M) was acquired and assessed by two radiologists with the MRI Knee Osteoarthritis Score (MOAKS). Overall MOAKS scores were created for Bone Marrow Lesions (BML), Cartilage Degradation (CD) and effusion/Hoffa synovitis (tSyn). Type II collagen cleavage products (CTX-II) were determined by ELISA. Clinical scoring was performed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) for pain levels (WOMAC_P), Hospital Anxiety and Depression Scale (HADS), Body mass index (BMI) and pain sensitisation with pain pressure thresholds (PPT) of the patella by Quantitative Sensory Testing (QST).

Results: The mild OA group had a mean age of 63 +/-9 yr and the advanced OA group 69 +/-9 yr. The advanced OA group had higher levels of pain, with a mean WOMAC_P of 58 +/- 22 compared with the mild OA group who had a mean WOMAC_P of 40 +/-22. WOMAC_P correlated with the total number of regions with cartilage damage (nCD) (R=0.225, p=0.033) and total number of BMLs (nBML) (R=0.195, p=0.065) using BMI, age and HADS as covariates. Levels of CTX-II correlated with tSyn (R=0.313, p=0.03), nBML (R=0.252, p=0.019), number of osteophytes (R=0.33, p=0.002) and nCD (R=0.218, p=0.042), using BMI and age as covariates. The correlation for urinary CTX-II with tSyn (p=0.006) is shown in Figure 1 using a partial linear regression analysis of MOAKS, BMI and age. We also found CTX-II correlated with lesion load scores (total number of lesions multiplied by MOAKS size by% damage scores) for CD (R=0.277, p=0.009) and BML (r=0.308, p=0.004). PPT correlated with patella MOAKS scores for nBML (R=-0.221, p=0.038) and nCD (R=-0.279, p=0.009), with HADS, BMI and age as covariates.

Conclusion: There is a direct correlation between the degree of cartilage damage and BMLs with pain in OA. Type II collagen degradation products were higher when there was more severe MRI-detected synovitis, BMLs and cartilage damage in the knee joint, suggesting that the source of enzymes degrading type II collagen in OA, including matrix metalloproteinases, are also likely to be produced by synovium and bone (1) and not just cartilage, as previously hypothesised in other studies. There was also a correlation between pain sensitisation and frequency of BMLs and cartilage degradation, suggesting that molecular mediators of pain sensitisation, which we have shown are produced by BMLs (1), are a cause of patient-reported OA pain.

REFERENCES:

[1] Kuttapitiya, et al. Annals Rheumatic Diseases, 2017; 76(10): 1764-73

Figure 1

Acknowledgement: We acknowledge funding from The Rosetrees' Trust and the National Institute for Health Research (NIHR) UK, for funding this project

Disclosure of Interests: Nidhi Sofat Grant/research support from: Prof Sofat has received Honoraria from Pfizer, Consultant for: Prof Sofat has received Honoraria from Pfizer, Vivian Ejindu: None declared, Christine Heron: None declared, Lena Assi: None declared, Anasuya Kuttapitiya: None declared, Guy Whitley: None declared, Soraya Koushesh: None declared, Abiola Harrison: None declared, Franklyn Howe: None declared

DOI: 10.1136/annrheumdis-2019-eular.2623

OP0198

MRI-DETECTED STRUCTURAL ABNORMALITIES AND DEVELOPMENT OF INCIDENT RADIOGRAPHIC KNEE OSTEOARTHRITIS OVER 10 YEARS OF FOLLOW-UP

C. Kent Kwok¹, Frank Roemer², Leena Sharma³, Erin Ashbeck⁴, Chengcheng Hu⁴, Ali Guermazi⁵, For the Biomarkers of Early Arthritis of the Knee (BEAK) Investigators. ¹University of Arizona, Tucson, United States of America; ²University of Erlangen-Nuremberg, Erlangen, Germany; ³Northwestern University, Chicago, United States of America; ⁴University of Arizona, Tucson, United States of America; ⁵Boston University, Boston, United States of America

Background: Structural joint pathology on MRI has been found in knees without radiographic evidence of osteoarthritis (OA). We have previously shown that structural abnormalities on MRI may be precursors of disease and associated with the detection of incident radiographic knee OA (ROA) up to 2 years later, and in some circumstances up to seven years later. The prognostic value of structural abnormalities on MRI for knee OA, however, is unknown.

Objectives: Estimate the probability of incident ROA over 10 years of follow-up, according to structural abnormalities detected on baseline MRIs.

Methods: A subcohort of participants (862 knees, one knee/person) from the Osteoarthritis Initiative (OAI) with at least one knee at risk of developing ROA (i.e., Kellgren-Lawrence (KL) 0,1 at baseline) was randomly selected. MRI-detected structural features of the knee were assessed by expert readers using the MRI Osteoarthritis Knee Score (MOAKS). Participants underwent bilateral posteroanterior fixed-flexion weight-bearing knee radiography at baseline and annually through year 4, and then every two years until year 10. Radiographs were centrally read for KL grade, with ROA defined as KL₂ or greater. Survival was estimated with the Turnbull non-parametric maximum likelihood estimator, a generalization of Kaplan Meier curves for interval censored data. Survival curves were compared using a log rank permutation test available in the R package interval. Hazard ratios were estimated using Cox models fit using the R package icenReg, designed for interval censored data. Features were considered one at a time, with no adjustments.

Results: Knees with any of the following structural abnormalities had higher estimated probabilities for the development of radiographic OA within two, four and 10 years of follow-up: effusion-synovitis, Hoffa-synovitis, bone marrow lesions in the medial compartment and whole knee, surface area and full thickness cartilage damage in the medial compartment and whole knee, and medial meniscal extrusion (Table 1). Differences in the probability for the development of ROA within two, four, and 10 years of follow-up were significant (pointwise 95% confidence intervals did not include 0), between knees without the abnormality and knees in the most severe category for all features, with one exception at the two-year follow-up. All of these abnormalities were significantly associated with time to ROA over 10 years of follow-up.

Table 1. Baseline MRI-Detected Structural Abnormalities and Incident Radiographic Osteoarthritis

MRI-detected abnormalities at baseline	Estimated Probability of Radiographic OA				P value*	Hazard Ratio	(95% CI)
	Knees	Within 2 years	Within 4 years	Within 10 years			
Effusion-synovitis					<.0001		
Physiologic amount	692	0.06	0.10	0.27		1.00	ref
Small	146	0.15	0.31	0.46		2.11	(1.81, 2.40)
Medium/Large	24	0.48	0.62	0.67		5.10	(3.55, 7.34)
Hoffa-synovitis					<.0001		
Normal	593	0.05	0.11	0.25		1.00	ref
Mild	248	0.16	0.24	0.44		1.97	(1.72, 2.26)
Moderate/Severe	21	0.43	0.43	0.54		4.09	(2.75, 6.07)
BML, Medial Max Score					<.0001		
0: none	733	0.08	0.13	0.27		1.00	ref
1: <33%	110	0.12	0.19	0.49		1.82	(1.54, 2.15)
2/3: >=33%	19	0.39	0.57	0.59		3.82	(2.49, 5.86)
BML, Whole Knee Max Score					<.0001		
0: none	339	0.06	0.10	0.21		1.00	ref
1: <33%	333	0.08	0.13	0.33		1.43	(1.22, 1.67)
2: 33-66%	143	0.14	0.25	0.43		2.14	(1.76, 2.57)
3: >66%	47	0.34	0.41	0.56		3.25	(2.49, 4.24)
Cartilage Damage, Surface Area, Medial Max Score					<.0001		
0: none	558	0.09	0.12	0.21		1.00	ref
1: <10%	146	0.05	0.12	0.36		1.63	(1.38, 1.94)
2: 10-75%	158	0.19	0.28	0.56		2.85	(2.45, 3.32)
Cartilage Damage, Full Thickness, Medial Max Score					<.0001		
0: none	824	0.09	0.15	0.30		1.00	ref
1/2: Any	48	0.18	0.35	0.57		2.70	(2.17, 3.36)
Cartilage Damage, Surface Area, Whole Knee Max Score					<.0001		
0: none	146	0.04	0.06	0.13		1.00	ref
1: <10%	235	0.03	0.06	0.18		1.41	(1.05, 1.90)
2: 10-75%	454	0.13	0.21	0.43		3.67	(2.81, 4.80)
3: >75%	27	0.43	0.43	0.66		8.66	(3.40, 13.86)
Cartilage Damage, Full Thickness, Whole Knee Max Score					<.0001		
0: none	574	0.07	0.11	0.25		1.00	ref
1: <10%	167	0.11	0.20	0.39		1.73	(1.47, 2.02)
2/3: >10%	121	0.18	0.28	0.52		2.43	(2.04, 2.90)
Meniscus Extrusion, Medial					<.0001		
<2 mm	677	0.06	0.12	0.24		1.00	ref
2: 2-3 mm	141	0.19	0.32	0.55		2.51	(2.15, 2.97)
2/3: >3 mm	44	0.20	0.25	0.55		2.88	(2.27, 3.66)

*Asymptotic Logrank k-sample test (permutation form), Sun's scores

Conclusion: Our results demonstrate the prognostic value of effusion-synovitis, Hoffa-synovitis, bone marrow lesions, cartilage damage, and meniscal extrusion