Disclosure of Interests: Sahil Mahajan: None declared, Zhengfeng Yang: None declared, Elisabeth Mellins Grant/research support from: Novartis and GlaxoSmithKline., roberta faccio: None declared
DOI: 10.1136/annrheumdis-2019-eular.2846

FRIDAY, 14 JUNE 2019

Remission – the holy grail? Looking across diseases

OP0330

COMPARISON OF THE EFFECTS OF DORIS REMISSION AND LUPUS LOW DISEASE ACTIVITY STATE (LLDAS) ON DISEASE OUTCOMES IN A MULTINATIONAL PROSPECTIVE STUDY

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Background: The Definitions of Remission in SLE (DORIS) group has proposed multiple definitions of remission, but these are infrequently attained and have not been prospectively evaluated in relation to protection from damage accrual. In contrast, the Lupus Low Disease Activity State (LLDAS) is more attainable, and has been shown to be associated with improved patient outcomes.

Objectives: To compare the attainability, and association with outcomes, of LLDAS and remission in a prospective multicentre study.

Methods: A prospective multinational cohort study was undertaken in 13 centres between 2013-2017. Time dependent Cox proportional hazards models were used to compare LLDAS and DORIS definitions of remission in terms of impact on disease flares and damage accrual.

Results: 1735 SLE patients were recruited, and followed for (mean±SD) 2.2±0.9 years, totalling 12,717 visits. LLDAS was achieved in 47.2% of observed visits. In contrast, remission was achieved in 1.1%-15.4% of visits depending on the stringency of remission definition. LLDAS attainment at any visit was associated with significantly reduced subsequent flare (HR 0.65, 95%CI 0.56-0.75, p<0.001) and damage accrual (HR 0.59, 95%CI 0.45-0.76, p<0.001). In contrast, only the least stringent remission definition was associated with reduced damage accrual (HR 0.58, 95%CI 0.39-0.88, p 0.01). Only remission definitions including serological remission were significantly associated with reduction in subsequent flares. Patients who spent ≥50% of their observed time in LLDAS had reduction in damage accrual (HR 0.54, 95% CI 0.42-0.70, p<0.001) compared to patients with <50% of observed time in LLDAS; again, only the least stringent remission definition, or the related definition excluding serology, were associated with reduced damage (HR 0.59, 95% CI 0.42-0.83, p 0.003; HR 0.69, 95% CI 0.48-0.99, p 0.05, respectively).

Conclusion: LLDAS was more attainable than any remission definition, whilst still conferring significant reduction in flares and damage accrual. Only the least stringent remission definitions could be shown to be associated with significantly lower damage accrual, likely reflecting a low frequency of remission attainment overall. LLDAS is a valid treatment target for SLE and is more achievable than remission.

Disclosure of Interests: Vera Golder: None declared, Eric F. Morand Grant/research support from: AstraZeneca, Bristol Myers Squibb, Janssen, Merck Serono, and UCB, Consultant for: AstraZeneca, Eli Lilly, Janssen, and Merck Serono, Speakers bureau: AstraZeneca, Rangi Kandane-Rathnayake: None declared, Molla Huq: None declared, Worawit Louthrenoo: None declared, Shue Fen Luo: None declared, Yeong-Jian Wu: None declared, Aisha Lateef: None declared, Sargunan Sockalingam: None declared, Sandra Navarra: None declared, Leonid Zamora: None declared, Laniyati Hamijoyo: None declared, Yasuhiro Katsumata: None declared, masayoshi harigai Grant/research support from: Tokyo Women's Medical University (TWMU) has received unrestricted research grants for Division of Epidemiology and Pharmacoepidemiology of Rheumatic Diseases from Ayumi Pharmaceutical Co. Ltd., Bristol Meyers Squibb, Chugai Pharmaceutical Co. Ltd., Nippon Kayaku Co. Ltd., Taisho Toyama Pharmaceutical Co. Ltd., Mitsubishi Tanabe Pharma Corp., and with which TWMU paid the salary of MH. MH has also received research grants from AbbVie Japan

GK, Eisai Co. Ltd., Takeda Pharmaceutical Co., Ltd., and Teijin Pharma Ltd., Madelynn Chan: None declared, Sean O'Neill: None declared, Fiona Goldblatt: None declared, Chak Sing Lau: None declared, Zhanguo Li: None declared, Alberta Hoi Grant/research support from: GSK, AstraZeneca, UCB and Merck Serono, Consultant for: Janssen Steering Committee, Speakers bureau: Novartis, Mandana Nikpour: None declared
DOI: 10.1136/annrheumdis-2019-eular.5136

OP0331

MAGNETIC RESONANCE IMAGING TENOSYNOVITIS AND OSTEITIS ARE INDEPENDENT PREDICTORS OF RADIOGRAPHIC AND MRI DAMAGE PROGRESSION IN RHEUMATOID ARTHRITIS PATIENTS IN CLINICAL REMISSION

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Background: Progression of structural joint damage occurs in 20-30 % of patients with rheumatoid arthritis (RA) in clinical remission¹. Magnetic resonance imaging (MRI)-detected synovitis and in particular osteitis/bone marrow edema (BME) are known predictors of structural progression in both active RA and in remission, but the predictive value of adding MRI tenosynovitis assessment as potential predictor in patients in clinical remission has not been investigated.

Objectives: To investigate the predictive value of baseline MRI inflammatory and damage parameters on 2 year MRI and X-ray damage progression in an RA cohort in clinical remission, following MRI and conventional treat-to-target (T2T) strategies.

Methods: 200 RA patients in clinical remission (DAS28-CRP<3.2 and no swollen joints) on conventional DMARDs, included in the randomized IMAGINE-RA trial² (conventional DAS28 + MRI-guided T2T strategy targeting absence of BME vs conventional DAS28 guided T2T strategy) had baseline and 2 years contrast-enhanced MRIs of the dominant wrist and 2nd-5th MCP joints and X-rays of hands and feet performed, which were evaluated with known chronology by two experienced readers according to the OMERACT RAMRIS scoring system and Sharp/van der Heijde method, respectively.

The following potentially predictive baseline variables: MRI BME, synovitis, tenosynovitis, MRI and X-ray erosion and joint space narrowing (JSN) score, CRP, DAS28, smoking status, gender, age and patient group were tested in univariate logistic regression analyses with 2-year progression in MRI combined damage score, Total Sharp Score (TSS), and MRI and X-ray JSN and erosion scores as dependent variables. Variables with p<0.1, age, gender and patient group were included in multivariable logistic regression analyses with backward selection.

Results: Based on univariate analyses MRI BME, synovitis, tenosynovitis, x-ray erosion and JSN, gender and age were included in subsequent multivariable analyses. Independent MRI predictors of structural progression were BME (MRI progression) and tenosynovitis (MRI and X-ray progression), see table.

Dependent variables, progression ≥1 from baseline to month 24 ^a						
		MRI			X-ray	
		MRI Erosion	MRI JSN	MRI combined damage score	X-ray Erosion	X-ray JSN
Explanatory variables	MRI BME	1.13 (1.06-1.21) p<0.001	1.18 (1.08-1.29) p<0.001	1.22 (1.12-1.33) p<0.001		
	MRI Tenosynovitis	1.13 (1.03-1.25) p=0.01	1.21 (1.04-1.40) p=0.01	1.13 (1.02-1.26) p=0.02		1.10 (1.00-1.21) p=0.04
	Age				0.96 (0.93-0.99) p=0.007	

^a: Odds Ratio (95% confidence interval; CI) p-value;

MRI combined damage score: sum score of MRI erosion and JSN scores.

Conclusion: This trial is the first to report that MRI tenosynovitis independently predicts both X-ray and MRI damage progression in RA patients in clinical remission. Further studies are needed to confirm MRI-determined tenosynovitis as predictor of progressive joint destruction in RA clinical remission.

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Acknowledgement: AbbVie for financial study support

Disclosure of Interests: Signe Møller-Bisgaard Grant/research support from: Grants and non financial support from AbbVie during the conduct of the study, Speakers bureau: BMS, Kim Hørslev-Petersen Grant/research support from: AbbVie during the conduct of the study, Bo Ejbjerg: None declared, Merete L. Hetland Grant/research support from: BMS, MSD, AbbVie, Roche, Novartis, Biogen, Pfizer, Consultant for: Eli Lilly, Speakers bureau: Orion Pharma, Biogen, Pfizer, CellTrion, Merck, Samsung Bioepis, Lykke Ørnbjerg Grant/research support from: Unrestricted grant: Novartis, Daniel Glinatsi: None declared, Jakob Møllenbach Møller: None declared, Mikael Boesen Grant/research support from: Image Analysis Group, Eli Lilly, UCB, AbbVie, Esaote, Kristian Stengaard-Pedersen: None declared, Ole Madsen Grant/research support from: Sobi, AbbVie, Merck Sharp and Dohme, Pfizer, Eli Lilly, Celgene, Novartis, UCB, Sanofi Aventis, Roche, Amgen and BMS, Bente Jensen: None declared, Jan Villadsen: None declared, Ellen Margrethe Hauge Grant/research support from: Have received grants from Roche and Novartis, outside the submitted work., Speakers bureau: Have received personal fees from MSD, Pfizer, UCB and Sobi, Philip Bennett Grant/research support from: Eli Lilly, Merck Sharp and Dohme, Novartis, Oliver Hendricks Grant/research support from: AbbVie, Novartis, Karsten Asmussen: None declared, Marcin Kowalski: None declared, Hanne Merete Lindegaard: None declared, Henning Bliddal Grant/research support from: AbbVie, Oak Foundation, Niels Steen Krogh: None declared, Torkell Ellingsen: None declared, Agnete Nielsen: None declared, Lone Balding: None declared, Anne Grethe Jurik: None declared, Henrik Thomsen: None declared, Mikkel Østergaard Grant/research support from: Abbvie, Celgene, Centocor, Merck, Novartis, Consultant for: Abbvie, BMS, Boehringer-Ingelheim, Celgene, Eli Lilly, Hospira, Janssen, Merck, Novartis, Novo, Orion, Pfizer, Regeneron, Roche, and UCB, Speakers bureau: Abbvie, BMS, Boehringer-Ingelheim, Celgene, Eli Lilly, Hospira, Janssen, Merck, Novartis, Novo, Orion, Pfizer, Regeneron, Roche, and UCB

DOI: 10.1136/annrheumdis-2019-eular.2006

FRIDAY, 14 JUNE 2019

Complement and autoimmunity – emerging therapeutic opportunities

OP0332

COMPLEMENT FACTOR EXPRESSION AND ACTIVATION IN OSTEOARTHRITIS JOINT COMPARTMENTS

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Background: Several studies have identified a central role for the activation of the complement system in the pathogenesis of OA, finding an abnormally high expression and activation of complement in human osteoarthritic joints and the specific contribution of complement (C) components 5 and 6 and the membrane attack complex (MAC) (1). The complement system consists of several proteins which contribute to an enzymatic cascade ending in lysis. Two main, different pathways converge into C3 factor activation. In the classical pathway C4 is involved, while in alternative pathways Factor-b (FB) is involved.

Objectives: The aim of this study was to investigate the expression of complement factors (C3, C4 and FB) and activation fragments (C3a, C5a, FBa, MAC) in OA joint tissues.

Methods: Osteochondral biopsies from 33 patients (16 OA, 12 Rheumatoid Arthritis-RA and 15 Posttraumatic cases-PT) who underwent knee, hip or shoulder arthroplasty were collected. Immunohistochemistry and quantitative Imaging analysis were performed to analyze C3, C4 and CFB expression. Cartilage pathology was evaluated utilizing Mankin score. Chondrocytes, synoviocytes, cartilage and synovial biopsies were obtained from 11 OA patients undergoing joint replacement surgery. Cultures were set up with or without pro-inflammatory (IL-1 β) stimulus. Culture supernatants were analyzed for C3a, C5a, CFBa and C5b-9 production using enzyme-linked immuno-sorbent assay (ELISA). Statistical analysis was performed utilizing Wilcoxon matched pairs test and Mann Whitney's test, using Graph Pad Prism software.

Results: In osteochondral biopsies, C factor expression was located in bone marrow and in a few subchondral bone cells. C3 was the most expressed factor in all

patient subtypes while factor C4 had a very low expression, except for some sporadic cases. (OA: C3 vs FactorB $p=0.0280$, C3 vs C4 $p=0.0005$; RA: C3 vs FactorB $p=0.0269$, C3 vs C4 $p=0.0005$; PT: C3 vs FactorB $p=ns$, C3 vs C4 $p=0.0001$) CFB was significantly augmented in PT and was not significantly different between OA and RA. C factors expression did not correlate with Mankin score or with the joint type (knee, hip or shoulder). Cell positivity was mainly present in the subchondral bone (bone marrow) whereas cartilage was almost negative. As to activation fragments, C3a was the most produced factor (vs C5a and CFBa $p<0.0005$) but no differences were found between cultured chondrocytes and synoviocytes (vs synovial tissue $p<0.0005$) and its production was not stimulated by proinflammatory stimulus. C5a production in cartilage was significantly higher than in chondrocytes and synovial tissue (both $p<0.0005$) but no differences were found between cartilage and synoviocytes. CFBa was induced by IL-1 β in synovial tissue. C5b-9 production was undetectable in chondrocytes and synoviocytes cell culture supernatants. In cartilage C5b-9 production was decreased by IL-1 β stimulus while in synovium it was increased, although not significantly.

Conclusion: Complement factors were expressed mainly in bone marrow and in a few subchondral bone cells, but not in cartilage. Complement activating fragments are produced by chondrocytes and synoviocytes. The dissimilar expression of activating fragments by different cell types could suggest various C activating mechanisms in joint tissues.

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Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2019-eular.5449

SATURDAY, 15 JUNE 2019

Novel autoantibodies in RMD: a neverending quest?

OP0333

RISING ACPA IGG VARIABLE DOMAIN GLYCOSYLATION PRE-DISEASE ASSOCIATES WITH AN INCREASE IN AUTOANTIBODY LEVELS AND THE DEVELOPMENT OF RHEUMATOID ARTHRITIS

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Background: Anti-citrullinated protein antibodies (ACPA) are present in the majority of rheumatoid arthritis (RA) patients (60-70%) and play a pivotal role in disease development¹. ACPA IgGs are unique in a way that they are abundantly N-glycosylated within their variable regions². These variable domain (V-domain) glycans are found on over 90% of ACPAs present in sera from RA-patients³. To undergo N-linked glycosylation, a consensus sequence in the protein backbone is required (N-X-S/T, where X $\neq$ P)⁴. Recently, it was shown that the N-linked glycosylation sites in ACPA-IgG V-domains are introduced during somatic hypermutation and that the introduction of such sites likely conveys a selective advantage to ACPA expressing B-cells⁵. However, it is currently unknown, whether ACPA-expressing B-cells already introduced glycosylation-sites into their V-domains before disease onset or when ACPA-V-domain glycosylation occurs.

Objectives: Investigate the appearance of ACPA V-domain glycosylation in pre-symptomatic individuals and RA patients.

Methods: In a case-control study, individuals (n=201) from the Medical Biobank, who were sampled before onset of symptoms (mean $\pm$ SEM predating time; 5.8 $\pm$ 0.3 years) (140 aCCP+ and 61 aCCP-), and after diagnosis of RA (n=99, 94 aCCP+ and 5 aCCP-) and randomly selected control samples (n=43, 3 aCCP+ and 40 aCCP-) were analyzed for their ACPA IgG V-domain glycosylation levels. ACPA IgGs were affinity purified, N-linked glycans released, and 2-AA labeled for further analysis using UHPLC⁶. Data calibration and integration was performed and a cut-off defined. Samples below the cut-off were determined as non-detectable and excluded from the analysis. The percentage V-domain glycosylation was calculated as described previously³. Statistical calculations were performed using SPSS.

Results: Our data indicated that ACPA IgG V-domain glycans are already present years before symptom onset, in pre-symptomatic individuals who subsequently will develop RA. Analysis of matched pairs showed a significant increase of ACPA V-domain glycosylation in RA patients compared to individuals pre-disease ($p<0.001$). The results showed that ACPA N-glycosylation was correlated with anti-CCP concentrations pre-disease ($r_s=0.504$, $p<0.001$), while no such association can be found after RA onset. Further, V-domain glycosylation levels increase closer to symptom onset.