reported to ameliorate arthritis in several mice models. Mechanistic target of rapamycin (mTOR) pathway and glutaminolysis activate cooperatively in the differentiation from myeloid progenitors to mature myeloid cells such as dendritic cells, macrophages, or osteoclasts as well as the activation of effector T cells and the differentiation of Th1 and Th17 cells. Although rapamycin has reported to facilitate the expansion of MDSCs and their immunosuppressive ability, the effect of the inhibitor of glutaminolysis on MDSCs is still unknown.

Objectives: The aim of this study is to evaluate the facilitative effects of the inhibition of mTOR pathway and glutaminolysis on MDSCs in a mouse model of rheumatoid arthritis.

Methods: Bone marrow (BM) cells from untreated Balb/c mice were cultured for 5 days under granulocyte-macrophage colony-stimulating factor (GM-CSF) stimulation with four patterns of drugs; 1) DMSO (control), 2) rapamycin (Rapa), 3) 6-Diazo-5-oxo-L-norleucine (DON; a glutamine antagonist), or 4) the combination of rapamycin and DON (Rapa +DON). Cultured BM cells were analysed by flow cytometry. Cultured MDSCs were isolated by manual MACS and analysed their immunosuppressive characters by co-culture with CFSE-dyed CD4⁺ T cells. Rapa or Rapa +DON were administered intraperitoneally to arthritic SKG mice induced by Zymosan A injection.

Results: We found that DON suppressed the differentiation of dendritic cells (DC) in a dose-dependent manner and the addition of Rapa on DON inhibited the differentiation of macrophages *in vitro*. The proportions of the phenotype of MDSCs were increased with administrations of Rapa or DON, and large part of them were Ly6G⁺ cells (the phenotype of polymorphonuclear MDSCs; PMN-MDSCs). Rapa ±DON significantly increased the expressions of TGF-β and PD-L1 and the inhibitory capacity of Ly6G⁺ PMN-MDSCs. Rapa +DON significantly suppressed arthritis more efficiently in SKG mice than Rapa *in vivo*. (see figure 1)

Conclusions: The combination of rapamycin and a glutamine antagonist facilitates the expansion of PMN-MDSCs *in vitro* and ameliorates arthritis in SKG mice *in vivo*.

Disclosure of Interest: None declared

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THU0099

MYELOID SIRTUIN 6 DEFICIENCY ACCELERATES EXPERIMENTAL AND HUMAN ARTHRITIS BY INCREASING MACROPHAGE INFILTRATION INTO SYNOVIUM

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Background: Rheumatoid arthritis (RA) is an autoimmune inflammatory disease of the joints and is characterised by immune cell infiltration, synovial hyperplasia, and destruction of cartilage and underlying bone¹. Myeloid derived monocytes and macrophages secrete a variety of cytokines such as tumour necrosis factor-α (TNF-α), interleukin (IL)-1β and IL-6, all of which perpetuate and amplify the vicious cycle of chronic inflammatory pathways². Indeed, macrophage numbers in the synovium and serum levels of monocyte-derived cytokines correlate well with clinical symptoms and degree of joint damage in RA³.

Objectives: We recently reported that myeloid sirtuin 6 (Sirt6) is a critical determinant of phenotypic switching and the migratory responses of macrophages⁴.

Given the prominent role of macrophages in rheumatoid arthritis (RA) pathogenesis⁵, we tested whether myeloid Sirt6 deficiency affects the development and exacerbation of RA.

Methods: Arthritis was induced in wild type and myeloid Sirt6 KO (mS6KO) mice using collagen-induced and K/BxN serum transfer models. Peripheral blood mononuclear cells (PBMC) and synovial fluid macrophages were obtained from patients with RA and osteoarthritis and used for comparisons of Sirt6 expression and inflammatory activities.

Results: Based on clinical scores, ankle thickness, pathology and radiology, arthritis was more severe in mS6KO mice relative to wild type with a greater accumulation of macrophages in the synovium. Consistently, myeloid Sirt6 deficiency increased the migration potential of macrophages toward synovial cells-derived chemoattractants. Mechanistically, Sirt6 deacetylates forkhead box protein O1 to trigger its nuclear export and proteasomal degradation. Lastly, PBMC and macrophages isolated from RA patients exhibited lower Sirt6 expression compared with those from osteoarthritis patients or healthy subjects and their Sirt6 activity was inversely correlated with disease severity of the patients.

Conclusions: Our data identify a role of myeloid Sirt6 in clinical and experimental RA and suggest that myeloid Sirt6 may be an intriguing therapeutic target.

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THURSDAY, 14 JUNE 2018

Rheumatoid arthritis – prognosis, predictors and outcome

THU0100

WORK IMPAIRMENT IN RHEUMATOID ARTHRITIS IS HIGHLY CORRELATED WITH DEPRESSION

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Background: Work outcomes are highly relevant in rheumatoid arthritis. Almost a third of people are no longer in employment by 2 years after diagnosis. Remaining in the workforce has positive attributes in terms of health outcome and quality of life.

Objectives: We set out to study the relationship between work and depression in rheumatoid arthritis.

Methods: We used routinely collected data from a hospital rheumatoid arthritis cohort that has systematically collected longitudinal data on disease measures, mental health, and work impairment. The Work and Social Adjustment Scale was used to estimate work impact, and we used question 2 (scale 0–8, above 6 indicating severe impairment) for analyses. Mood was assessed using the PHQ2. Cross sectional analyses were used to describe the relationship between work impairment and depression, adjusting for disease severity factors. We then analysed the temporal relationship between work impairment and mood.

Results: In total 283 patients had data available for analysis. Mean age was 53 years (SD 15), 81% were female, median disease duration 6 years (IQR 0 to 10). 74% were seropositive (RF or CCP), mean baseline DAS28 score 3.8 (SD 1.7), baseline HAQ 1.2 (SD 0.9). At baseline 69% reported no depression, 13% reported some symptoms, 18% had probable major depression. 72% of patients reported some degree of work impairment, 14% reported severe impairment. There was a strong relationship between baseline depressive symptoms and work impairment: coefficient 2.4, 95% CI 1.7 to 3.0, p<0.001. Adjusting for age, gender, DAS28, HAQ: 1.3, 95% CI 0.5 to 2.0, p=0.004. Over time work impairment increased (linear regression coefficient: 0.2 per year 95% CI 0.1 to 0.4), see figure 1. People with baseline low mood had an accelerated worsening of work impairment.

Conclusions: Work impairment is highly prevalent in contemporary rheumatoid arthritis patients. It is significantly correlated with mental health, even after adjusting for disease severity factors. Baseline mental health also predicts progression of work impairment. The relationship is likely bidirectional, and future research is justified to evaluate whether mental health interventions could improve work outcomes.

Disclosure of Interest: None declared

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THU0101 TISSUE METABOLITE OF TYPE I COLLAGEN, C1M, AND CRP PREDICTS STRUCTURAL PROGRESSION OF RHEUMATOID ARTHRITIS

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Background: Biomarkers of rheumatoid arthritis (RA) disease activity typically measure inflammation or autoimmunity (e.g. CRP, rheumatoid factor (RF)). Another class of biomarkers are structural proteins of the joint. C1M and C3M, metabolites of type I and III collagen, are such biomarkers. These biomarkers have previously been documented to provide additional value as compared to standard inflammation biomarkers, for prognosis and prediction of response to treatment¹.

Objectives: We investigated the relationship of high serum levels of C1M or C3M to radiographic progression, and benchmarked to CRP levels and RF status, demonstrated to be associated with structural progression².

Methods: Placebo treated patients of the OSK123 studies (Ph3 clinical trials testing efficacy of fostamatinib) with baseline serum biomarkers C1M, C3M, CRP and RF were included ($n_{BL}=474$). Van der Heijde mTSS was calculated at baseline and 24 week ($n_{24}=264$). Progression was defined as moderate or rapid (≥ 0.5 or ≥ 5 mTSS units/y). Patients were divided into subgroups; low, high or very high C1M, C3M and CRP (above/below median and highest quartile), or RF negative, positive and high positive (≥ 110 U/L)². Difference in clinical parameters were analysed by Mann-Whitney/Chi-squared tests, and multivariate predictive calculations by **Classification And Regression Tree** analysis including covariates (age, BMI, gender and disease activity assessment scores).

Results: High C1M, C3M and CRP levels were significantly associated with measures of disease activity ($p<0.05$) and patient reported scores ($p<0.05$). RF_{pos} was also associated with disease active scores ($p<0.05$). RF_{pos} and CRP ($p<0.001$), as well as C1M and C3M ($p<0.05$), were significantly associated with mTSS at baseline. For prognostic measures, there were 2.5 and 4-fold as many rapid progressors in the C1M_{high} and CRP_{high} ($p<0.05$), and in the C1M_{veryhigh} and CRP_{veryhigh} groups ($p<0.001$) compared C1M_{low} and CRP_{low}, respectively. C1M and CRP performed similarly in the predictive analysis with AUCs of 0.67 and 0.69 (table 1). The best model involving C1M in predicting rapid progressor included BMI, SJC and HAQ (AUC 0.85), whereas the best model for CRP included CRP, BMI, SJC and HAQ (AUC 0.85). C3M and RF did not provide prognostic value.

Model description	Progressors (delta mTSS ≥ 0.5 units per year)		Rapid progressors (delta mTSS ≥ 5 units per year)	
	AUC Specificity Sensitivity Correctly identified	Model parameters	AUC Specificity Sensitivity Correctly identified	Model parameters
C1M alone	0.600 59.7 53.8 56.7	C1Mveryhigh C1Mhigh	0.672 83.1 45.8 64.5	C1Mveryhigh C1Mhigh
C1M with demo., clinical ass., and X-ray	0.732 87.8 40.5 64.1	C1Mveryhigh Age BMI Disease duration HAQ ERN JSN	0.849 78.4 73.9 76.2	C1Mveryhigh BMI Disease duration HAQ
CRP alone	0.594 85.1 28.8 56.9	CRPveryhigh CRPhigh	0.687 84.0 50 67.0	CRPveryhigh CRPhigh
CRP with demo., clinical ass., and X-ray	0.717 76.1 51.9 64.0	CRPhigh Age BMI Disease duration SJC HAQ	0.847 53.4 95.7 74.2	CRPhigh BMI SJC HAQ

Conclusions: Of the four markers analysed only C1M and CRP were associated with structural progression. They seem to perform equally well, but reflect two different aspects of disease pathogenesis (tissue turnover vs. inflammation), thus may provide individual, but supplementary, information. These simple measures may be important for enrichment of clinical trials with structural progressors.

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THU0102 HIGH RATES OF RESIDUAL DISEASE ACTIVITY DESPITE CURRENT THERAPIES IN A REAL LIFE RHEUMATOID ARTHRITIS COHORT: DATA FROM 1096 PATIENTS

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Background: It is unclear if the widespread use of biologic DMARDs (bDMARDs) and the implementation of the treat to target approach have led to better disease control in patients with rheumatoid arthritis (RA) in daily clinical practice.

Objectives: To study the longitudinal changes in disease activity in a large, real life, longitudinal RA cohort.

Methods: Multicenter (11 hospitals, 3 private offices), prospective, RA epidemiological study in Greece. Demographics, disease characteristics, treatments and co-morbidities were collected via a web-based platform in registered patients at baseline and one year after their 1st visit.

Results: 1,096 RA patients with available paired evaluations one year apart (mean interval: 13.4 $\pm$ 3.6 months) were included (women: 78%, mean age: 62.8 years, mean disease duration: 11 years, RF and/or anti-CCP positive: 60%, mean HAQ: 0.44 $\pm$ 0.56). At baseline, 50% (n=548) of patients were on conventional DMARDs (csDMARDs) alone, 35% on cs- and b-DMARD combination (n=379) and 11% on bDMARD monotherapy (n=124). Among bDMARD treated patients, 60% were