OP0201

INCREASED RISK OF DEMENTIA IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Background: Systemic lupus erythematosus (SLE) is a chronic inflammatory disease that can affect any organ of the body. Nervous system involvement of SLE lead to a variety of neurologic and psychiatric manifestations, which are called neuropsychiatric lupus. Cognitive dysfunction may appear as part of neuropsychiatric lupus. There are several papers on the increase in dementia risk in SLE patients, but data are not sufficient and there is little data on whether SLE affects dementia differently depending on the dementia subtype.

Objectives: We evaluate dementia incidence and risk in SLE patients in a nationwide population-based cohort and determine whether the risk is different for each dementia subtype.

Methods: We identified patients aged 40 years or more, with systemic lupus erythematosus between 2008 and 2014 using the database of the National Health Insurance Service (NHIS) of south Korea. Patients who had previously been diagnosed with dementia were excluded from the study. A total of 11,288 SLE patients and 56,440 control subjects with a 1:5 age- and sex-matching were included in the study. The primary outcome of the study was incident dementia, which was defined by an ICD-10 code and the use of dementia medications. Kaplan-Meier curves and Cox proportional hazards regression analysis were used for the analysis.

Results: The incidence rate of dementia was higher in SLE cohort (3.90 per 1,000 person-years) than control cohort (2.73 per 1,000 person-years). Incidence rates of Alzheimer disease and vascular dementia were also higher in SLE cohort than control. SLE patients had a higher risk of dementia compared to control cohorts without SLE (crude hazard ratio 1.43, 95% CI 1.25-1.63). In patients with SLE, the risk of Alzheimer's disease was 1.4 times higher and the risk of vascular dementia 1.6 times higher than non-SLE control.

Conclusion: In this nationwide population-based cohort study, SLE patients had a 1.4-fold higher risk of incident dementia compared to patients without SLE. Further studies are warranted to identify mechanisms of increased risk of dementia in SLE patients. Monitoring of dementia incidence in SLE patients is needed in clinical practice.

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OP0202

STRESS-ACTIVATED MIR-204 GOVERNS SENESCENT PHENOTYPES OF CHONDROCYTES TO PROMOTE OSTEOARTHRITIS DEVELOPMENT

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Background: A progressive loss of cartilage matrix leads to the development of osteoarthritis (OA). Matrix homeostasis is disturbed in OA cartilage as the result of reduced production of cartilage-specific matrix and increased secretion of catabolic mediators by chondrocytes. Chondrocyte senescence is a crucial cellular event contributing to such imbalance in matrix metabolism during OA development.

Objectives: We sought to identify a previously unknown, senescence-associated signaling pathway in chondrocytes linked to major OA cartilage manifestations such as PG loss and cartilage degeneration.

Methods: We particularly aimed to screen miRNAs whose inhibition could effectively modulate senescent phenotypes of chondrocytes to treat OA. We investigated the regulatory mechanisms of miR-204 under various stress-eliciting stimuli in primary cultured human and mouse chondrocytes. We examined the in vivo effects of miR-204 overexpression and its antagonism in surgically induced OA mouse models. DMM surgery was used to induce posttraumatic OA in 12-week-old mice. Small RNAs were delivered to mouse knee joints by intra-articular injection. Various OA manifestations including cartilage destruction, subchondral bone sclerosis, osteophyte maturity, and synovial inflammation in mice were histologically inspected.

Results: We identify miR-204 as a senescence-associated microRNA (miRNA) which is markedly upregulated in OA cartilage. The upregulated miR-204 simultaneously targets multiple components of the sulfated proteoglycan (PG) biosynthesis pathway, effectively shutting down PG anabolism. Ectopic expression of the miR-204 in joints triggers spontaneous cartilage loss and OA development, whereas inhibition of miR-204 ameliorates experimental OA, with concomitant

recovery of PG synthesis and suppression of inflammatory senescence-associated secretory phenotype (SASP) factors in cartilage

Conclusion: we unravel a stress-activated senescence pathway that underlies disrupted matrix homeostasis in OA cartilage.

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OP0203-HPR

EVALUATION OF A 10-WEEK PROGRESSIVE RESISTANCE TRAINING PROGRAMME FOR PEOPLE WITH INFLAMMATORY ARTHRITIS

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Background: Inflammatory Arthritis [IA] adversely affects well-being, function, fatigue and strength¹. Guidelines recommend people with IA should exercise to improve strength and cardiovascular fitness². In 2015, our team introduced an evidence-based Progressive Resistance Training Programme [PRT] for IA³.

Objectives: To evaluate the effectiveness of a PRT within a United Kingdom National Health Service setting.

Methods: A pre- to post-treatment evaluation was conducted. People with IA attending Rheumatology Physiotherapy were offered a supervised PRT (1 hour x 10 weeks); 7 exercises at 70-80% 1-repetition maximum (3 x 8-12 repetitions). Treatment outcomes included Health Assessment Questionnaire [HAQ], EQ5D-5L, 30s sit-to-stand [STS], Self-Efficacy (SARAH Trial) [SE], Grip Strength and FACIT-Fatigue [FACIT-F]. Changes in outcomes were analysed using Paired Samples t-tests and standardised mean difference (SMD).

Results: 201 patients commenced the programme between May 2015 and April 2019, with 121 participants providing complete pre-post HAQ data. Diagnoses included Rheumatoid Arthritis (n=149), Psoriatic Arthritis (n=42), Juvenile Idiopathic Arthritis (n=5), Enteropathic IA (n=2), Oligoarthritis (n=1), Reactive Arthritis (n=1) and Undifferentiated IA (n=1). Age (mean ± SD) = 56.8 ± 14.8 years; number of sessions attended = 7.7 ± 3.4.

There were no differences between those recorded as not completing the PRT (n=54; 72% women; age 55.0 ± 14.6 years; HAQ 0.99 ± 0.70) versus the others (n=147; 78% women; age 57.5 ± 14.8; HAQ 0.86 ± 0.65). A pragmatic decision was made to analyse all available data for each outcome.

Table 1. Analysis of PRT outcomes * Indicates clinical improvement.

Outcome measure	Pre-treatment	Post-treatment	Mean difference (95% CI)	p-value	Standardised mean difference (95% CI)
HAQ	0.83 ± 0.65	0.70 ± 0.67	-0.13 (-0.07, -0.19)	p<0.001	-0.20*
max score 3 (n=121)					(-0.46, 0.07)
EQ5D VAS	70.0 ± 16.3	76.7 ± 15.2	6.7 (9.4, 3.9)	p<0.001	0.42*
max score 100 (n=119)					(0.17, 0.68)
STS	13.2 ± 4.9	16.2 ± 5.3	3.0 (3.6, 2.5)	p<0.001	0.59*
number in 30s (n=118)					(0.33, 0.85)
SE	52.3 ± 10.4	58.6 ± 8.0	6.3 (8.3, 4.4)	p<0.001	0.68*
max score 70 (n=117)					(0.41, 0.94)
Grip Strength kg force (n=62)	20.3 ± 9.4	23.6 ± 10.6	3.3 (4.8, 1.7)	p<0.001	0.33*
FACIT-F	30.9 ± 11.5	35.5 ± 12.0	4.6 (7.2, 2.1)	p=0.001	(-0.03, 0.68)
max score 52 (n=58)					0.39*
					(0.02, 0.76)

Conclusion: All outcome measures demonstrated statistically significant improvements. Notably, minimal clinically important differences were achieved in STS and FACIT-F. STS correlates to lower limb power, balance and endurance, and is a predictor of falls⁴. Fatigue significantly impacts function in people with IA⁵, often limiting confidence and willingness to participate in exercise activities⁶.

Effective evidence-based PRTs for people with IAs can be delivered by Physiotherapists. Improvements in function, wellbeing, self-efficacy, strength and fatigue are achievable, however, exploration of the clinical relevance of these observed changes is recommended. Further research exploring patients' perspectives of the PRT and adherence to long-term exercise is needed.

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OP0204

LUPUS COMPREHENSIVE DISEASE CONTROL IN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS: APPLICATION OF A NEW INDEX

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Background: The main outcomes in SLE patients management are represented by the remission achievement and chronic damage prevention. Even though activity and damage are intimately connected, to date indices including both these outcomes are not available.

Objectives: In the present study, we aimed at assessing the application of a new index, the Lupus comprehensive disease control (LupusCDC), including disease activity and chronic damage progression.

Methods: We performed a longitudinal analysis, including SLE patients according to ACR 1997 criteria, followed-up in the period between January 2014 and December 2018, and with at least one visit per year. Disease activity was assessed by SLE Disease Activity Index 2000 (SLEDAI-2K) and three different remission levels were evaluated, as reported in Table 1 (1).

Table 1. Remission levels considered in the study (1).

Remission level	Definition
Complete Remission (CR)	No clinical and serological activity (SLEDAI-2K=0) in corticosteroid-free and immunosuppressant-free patients (antimalarials allowed)
Clinical remission off-corticosteroids (CIR-GCoff)	Serological activity with clinical quiescent disease according to SLEDAI-2K in corticosteroid-free patients (stable immunosuppressive therapy and antimalarials allowed)
Clinical remission on-corticosteroids (CIR-GCon)	Clinical quiescent disease according to SLEDAI-2K in patients on prednisone 1–5 mg/day (stable immunosuppressants and antimalarials allowed)

Chronic damage was registered according to SLICC damage index (SDI). All the patients were evaluated at baseline (T0) and every 12 months (T1, T2, T3, T4). At each time-point, we calculated the prevalence of LupusCDC, defined as remission achievement plus absence of chronic damage progression in the previous one year. We calculated this outcome including separately the different remission levels.

Results: According with inclusion criteria, 172 SLE patients were evaluated in the present analysis [M/F 16/156, median age 49 years (IQR 16.7), median disease duration 180 months (IQR 156)]. At first assessment, we observed a mean±SD SDI value of 0.7±1.1. In details, 56 patients (32.5%) showed damage in at least one organ/system and the presence of damage was significantly associated with age ($p<0.0001$, $r=0.3$) and disease duration ($p=0.0003$, $r=0.3$). During the follow-up, we observed a significant increase in SDI values compared with T0 (T1: mean±SD 0.8±1.3, $p<0.0001$; T2: 0.8±1.4, $p<0.0001$; T3: 0.9±1.4 $p=0.0001$; T4: 1.0±1.5 $p<0.0001$).

In figure 1A and 1B we reported the proportion of patients achieving the different levels of remission and LupusCDC, respectively. In particular, the LupusCDC definition including CR was the most frequently detected in all time-points evaluated (T1: 18.0%; T2: 31.9%; T3: 27.9%; T4: 24.4%), with a significant difference at T2 [LupusCDC(CR) versus LupusCDC(CIR-GCoff), $p=0.0002$; LupusCDC(CR) versus LupusCDC(CIR-GCon) $p=0.0002$], T3 [LupusCDC(CR) versus LupusCDC(CIR-GCoff), $p=0.03$; LupusCDC(CR) versus LupusCDC(CIR-GCon)

$p=0.006$], T4 [LupusCDC(CR) versus LupusCDC(CIR-GCon), $p=0.002$]. No significant differences were found when comparing the prevalence of different remission levels and the prevalence of LupusCDC including the corresponding remission.

Conclusion: In the present analysis we proposed for the first time a new index including disease activity and chronic damage, in order to evaluate the proportion of SLE patients reaching a comprehensive disease control. We found that CR is most frequently associated with the absence of damage progression.

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Figure 1. Proportion of patients achieving one of the three levels of remission (A), and of patients reaching LupusCDC according with different remission levels (B).

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OP0205

PHASE I STUDY OF D-0120, A NOVEL URAT1 INHIBITOR IN CLINICAL DEVELOPMENT FOR HYPERURICEMIA AND GOUT

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Background: D-0120 is a novel oral selective uric acid transporter (URAT1) inhibitor being developed for the treatment of hyperuricemia and gout by blocking the reabsorption of uric acid (UA) within the renal proximal tubule, thereby reducing serum uric acid concentrations. As a novel URAT1 inhibitor, D-0120 is anticipated to have more potent serum UA reducing effect than the approved URAT1 inhibitor lesinurad, but with less toxicity and wider therapeutic window. The pharmacological potential of D-0120 for the treatment of hyperuricemia and gout was demonstrated in preclinical studies. The results of the in vitro hURAT1 expressed CHO cell model showed that the inhibitory activity of D-0120 is 150-fold more potent than lesinurad and slightly more potent than verinurad.

Objectives: The purpose of this dose escalation study is to evaluate the safety and tolerability of D-0120 in multiple ascending doses in healthy volunteer, to characterize the pharmacokinetics (PK) of D-0120 and to assess pharmacodynamic (PD) effects and determine the drug-drug interaction (DDI) effect of febuxostat and D-0120 in healthy volunteers.

Methods: This is a randomized, double blind, multiple ascending doses Phase I study of D-0120 in healthy volunteers conducted at one site. Thirty-two healthy eligible volunteers with serum uric acid level ≥ 4.5 mg/dL but within normal range at screening were enrolled and dosed with D-0120 within 4 different single agent cohorts for a period of 7 days. Each cohort had 8 subjects randomized at 3:1 ratio for D-0120:placebo. A fifth cohort of 8 healthy eligible volunteers were enrolled and dosed with 5 mg of D-0120 in combination with 40 mg of febuxostat over a period of 9 days. Evaluation of safety, PK and PD was conducted at various timepoints while the patients were in