intensity of chronic pain when awake and during sleep. These findings explain the excessive rate of syncope observed in the FM population during wakefulness, and the increased presence of CAP, PB and PLMs during sleep.
Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2017-eular.3365

WEDNESDAY, 14 JUNE 2017

Chondrocyte channels (role in mechanotransduction) or "channeling the chondrocyte"

OP0007 CCR2 INHIBITION ABROGATES IL-6–INDUCED ACTIVATION OF MATRIX METALLOPROTEINASES IN CARTILAGE

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Background: Interleukin 6 (IL-6) plays a crucial role in many rheumatic diseases, including osteoarthritis (OA) [1]. In cartilage, IL-6 activates chondrocyte catabolism by increasing the production of matrix-degrading enzymes, including matrix metalloproteinase 3 (MMP-3) and MMP-13, but it could have other roles.
Objectives: We aimed to identify new biological processes regulated by IL-6 in cartilage.
Methods: RNA-seq analysis (Illumina HiSeq platform) was used to determine biological pathways associated with IL-6/IL-6R (100 ng/ml) stimulation in mouse primary articular chondrocytes. Results were further validated by qPCR and western blot analysis. The effect of stimulation with CC chemokine ligand 2 (CCL2; 10 ng/ml), CCL7 and CCL8 (100 ng/ml) was investigated *in vitro* and *ex vivo* in mouse femoral head cartilage explants. The impact of targeted inhibition of CCL2 or CCL7 by siRNA or blockade of their common receptor CCR2 by a specific antagonist (RS-504393) was determined in IL-6–treated chondrocytes and/or cartilage explants.
Results: Transcriptomic analysis revealed overrepresentation of multiple functional clusters of genes in IL-6–stimulated chondrocytes, with strongly increased expression of signalling molecules and especially cytokines. Two of the 10 top genes upregulated by IL-6 were *Ccl7* (log2 fold change [FC] 2.33, adjusted p-value [p_{adj}] $=3.35\times10^{-62}$) and *Ccl2* (log2 FC 1.85, p_{adj} $=9.10\times10^{-26}$), which encode for CCR2 ligands. qPCR and western blot validations confirmed these results and revealed that IL-6 stimulation also increased the mRNA level of *Ccl8*, another CCR2 ligand not identified by RNA-seq analysis. CCL2 and CCL7 but not CCL8 activated extracellular signal-regulated kinase 1/2 and c-Jun N-terminal kinase signalling and increased MMP-3 and MMP-13 production and activation. CCR2 blockade but not the specific inhibition of CCL2 or CCL7 by siRNA, greatly abrogated the IL-6–induced catabolism *in vitro* and *ex vivo*.
Conclusions: We identified 2 chemokines, CCL2 and CCL7, as key targets of IL-6 in chondrocytes. Although their main role is to mediate monocyte/macrophage recruitment to the joint, their receptor, CCR2, is also strongly involved in IL-6–induced cartilage catabolism. These results suggest a novel mechanism by which CCL2/CCR2 and CCL7/CCR2 signalling could be involved in rheumatic diseases, especially OA [2].
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Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2017-eular.3359

OP0008 DEFICIENT AUTOPHAGY INDUCES CHONDROCYTE DYSFUNCTION THROUGH LAMIN A/C ACCUMULATION IN AGING AND OSTEOARTHRITIS

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Background: Aging-related Osteoarthritis (OA) is characterized by insufficient extracellular matrix synthesis and articular cartilage degradation. Autophagy is essential to maintain chondrocyte homeostasis by regulating the intracellular macromolecule and organelle turnover (1). Previous findings indicated that autophagy is defective in Aging and OA articular cartilage (2,3). However, the specific target/-s that regulates this homeostatic mechanism and affect cartilage integrity are still unknown.
Objectives: The objective of study is to identify targets regulating autophagy in human chondrocytes.
Methods: We performed quantitative proteomic analysis of Atg5 knockdown primary uman chondrocytes using iTRAQ (isobaric tags for relative and absolute quantitation) labeling coupled with on-line 2D LC/MS/MS. Protein identification and quantification were performed using Protein Pilot Software v 4.0. Each MS/MS spectrum was searched in the Uniprot/Swissprot database for *Homo sapiens*. Human chondrocytes and human cartilage from healthy, aged and OA patients were employed to confirm the role of the identified target by Western Blot (WB), Inmunofluorescence (IF) and Inmunohistochemistry (IHC). Importanly, CRISPR/Cas9 genome editing technology was used for mechanism of action studies.
Results: 24 out of 487 proteins were significantly altered ($p<0.05$) in response to defective autophagy. Cytoskeleton organization, collagen catabolism, oxidative stress, and aging pathways were affected. Interestingly, Lamin A/C, a nuclear protein implicated in cell senescence, was found upregulated under defective autophagy. Increased Lamin A/C expression was found in human chondrocytes with reduced autophagy. Furthermore, aged and OA human cartilage showed increased Lamin A/C expression. Induction of chondrocyte senescence by genetic deletion of Zinc Metalloproteinase STE24 (Zmpste24) via CRISPR-Cas9, lead to Lamin A/C accumulation, accompanied by a reduction of LC3 and increased chondrocyte death and mitochondrial dysfunction, suggesting that deficient autophagy is correlated with senescence of human articular cartilage.
Conclusions: Lamin A/C, a nuclear protein contributing to structural integrity to the nucleus and matrix was identified as candidate target for regulating cartilage function under defective autophagy, such as aging and OA. These results support the hypothesis that autophagy is decreased with aging. Therefore, targeting Lamin A/C might be a promising strategy to find novel therapeutics for cartilage aging and OA.
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Acknowledgements: This study was supported by Instituto de Salud Carlos III-Ministerio de Economía y Competitividad, Spain-CP11/00095 and Fondo Europeo de Desarrollo Regional (FEDER).
Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2017-eular.3819

WEDNESDAY, 14 JUNE 2017

Wearable technologies in 21st century healthcare

OP0009-HPR THE EFFECT OF AN 8-WEEK WATER EXERCISE PROGRAM ON ANAEROBIC EXERCISE CAPACITY IN CHILDREN WITH JUVENILE IDIOPATHIC ARTHRITIS

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Background: Anaerobic exercise capacity was reported to be lower in children with juvenile idiopathic arthritis (JIA) than healthy children. However, to our knowledge, there is no study focusing on improving anaerobic exercise capacity in JIA.
Objectives: To investigate the effect of an 8-week water exercise program, which was performed at the weekends, on anaerobic exercise capacity in children with JIA.
Methods: Forty-two children with JIA were divided into two groups as exercise and control. Prior to the study, anaerobic exercise capacity was measured performing a 30-second Wingate test. Deep water running was employed as the progressive water exercise program for the exercise group. Control group did not receive any additional treatment other than their usual care. Weekends were chosen for the exercise sessions considering the educational program of the children. Exercise intensity was set as moderate. Exercise intensity was determined with a wearable heart rate tracking system during the exercises. All children were reassessed regarding to anaerobic exercise capacity two months after the first assessment.
Results: All children completed the study without any adverse effects. Twenty-one children were in the exercise group, others were assessed as controls. No significant differences were determined between groups prior the study regarding to age, disease duration, height, weight, body-mass index, and anaerobic exercise capacity related parameters ($p<0.05$). While all anaerobic exercise capacity parameters improved in the exercise group, no improvement were seen in the control group. The in-group comparisons were shown at Table 1. The comparison of the changes between groups after 8 weeks were demonstrated at Table 2.

Table 1. In-group comparison before and after the study

	Before Median (IQR 25/75)	After Median (IQR 25/75)	p
Exercise Group (n=21)			
Peak Power (W)	354.73 (267.59/471.55)	441.3 (295.2/636.9)	**0.002***
Peak Power (W/kg)	6.74 (5.44/8.94)	7.7 (6.4/9.7)	**0.001***
Average Power (W)	291.5 (188.78/359.61)	360.0 (220.4/446.4)	**0.001***
Average Power (W/kg)	5.54 (4.07/6.88)	6.0 (4.8/7.4)	**0.002***
Control Group (n=21)			
Peak Power (W)	355.57 (225.43/463.62)	366.7 (236.3/447.8)	0.259
Peak Power (W/kg)	6.69 (5.80/7.83)	7.3 (6.1/8.1)	0.232
Average Power (W)	261.04 (181.68/351.27)	284.8 (187.8/373.0)	0.050
Average Power (W/kg)	5.29 (4.75/5.85)	5.5 (5.0/6.1)	0.076

Wilcoxon Test. IQR: Interquartile Range; W: watt; W/kg: watt/kilogram; *p<0.05.

Table 2. The differences in the groups after 8 weeks

	Exercise Group (n=21) Median (IQR 25/75)	Control Group (n=21) Median (IQR 25/75)	p
ΔPeak Power (W)	65.1 (23.8/107.1)	24.5 (-15.6/39.4)	**0.009***
ΔPeak Power (W/kg)	0.9 (0.3/1.6)	0.3 (-0.3/0.6)	**0.007***
ΔAverage Power (W)	41.4 (9.9/78.7)	17.3 (5/31.3)	**0.019***
ΔAverage Power (W/kg)	0.6 (0.3/1.3)	0.2 (-0.1/0.5)	**0.024***

Mann-Whitney U Test. IQR: Interquartile Range; Δ: Delta; W: watt; W/kg: watt/kilogram; *p<0.05.

Conclusions: The present study is the first study focusing on improving anaerobic capacity in children with JIA. According to our results, an 8-week water exercise program which is performed at the weekends might be beneficial to improve anaerobic exercise capacity in children with JIA.
Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2017-eular.5670

WEDNESDAY, 14 JUNE 2017

Assessment and management of osteoporosis

OP0010 EFFECT OF DENOSUMAB COMPARED WITH RISEDRONATE IN GLUCOCORTICOID-TREATED INDIVIDUALS: RESULTS FROM THE 12-MONTH PRIMARY ANALYSIS OF A RANDOMIZED, DOUBLE-BLIND, ACTIVE-CONTROLLED STUDY

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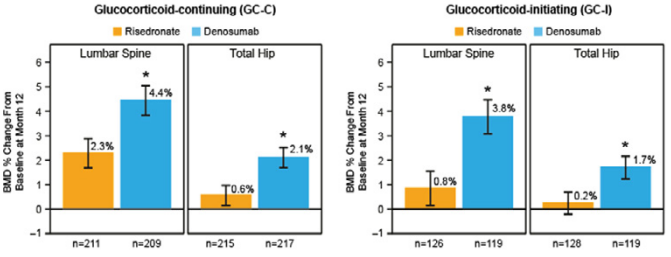
Background: Glucocorticoid (GC)-induced osteoporosis (GIOP) remains the most common secondary cause of osteoporosis. Despite approved therapies, many subjects do not receive GIOP prevention or treatment. There is increased RANKL and decreased osteoprotegerin (OPG) expression in patients with GIOP. Denosumab (DMAb) is a monoclonal antibody to RANKL. This study was designed to assess the safety and efficacy of DMAb compared with risedronate (RIS) in GC-treated individuals, in whom treatment guidelines advocate a GIOP intervention.
Objectives: The primary objective was to demonstrate, in separate GC-continuing (GC-C) and GC-initiating (GC-I) subpopulations, that DMAb was not inferior to RIS with respect to percentage change from baseline (%Δ) in lumbar spine (LS) bone mineral density (BMD) at 12 months. Secondary objectives were to assess superiority of DMAb over RIS with respect to %Δ in LS and total hip (TH) BMD at 12 months.
Methods: This was a phase 3, randomized, double-blind, double-dummy, active-controlled study to evaluate DMAb vs. RIS in GC-treated individuals for 24 months. Eligible subjects were women and men ≥18 yrs receiving GC therapy at a dose ≥7.5 mg prednisone daily or its equivalent for ≥3 months or <3 months prior to screening (GC-C and GC-I, respectively). All subjects <50 yrs were required to have a history of osteoporotic fracture. GC-C subjects ≥50 yrs were required to have a LS, TH, or femoral neck BMD T-score ≤-2.0; or a T-score ≤-1.0 with a history of osteoporotic fracture. Subjects were randomized 1:1 to SC DMAb 60 mg every 6 months or oral RIS 5 mg daily for 24 months. Subjects were to receive daily calcium (≥1000 mg) and vitamin D (≥800 IU) supplementation. Primary outcome was %Δ in LS BMD at 12 months (non-inferiority in GC-C and GC-I). Secondary outcomes included %Δ in LS and TH BMD at 12 months (superiority). The study remains blinded and is ongoing.
Results: A total of 795 subjects (505 GC-C and 290 GC-I) enrolled in the study. Baseline characteristics were balanced between treatment groups (Table). Non-inferiority and superiority with DMAb were demonstrated for both the GC-C and GC-I subpopulations, as indicated by significantly greater BMD gains compared with RIS at the LS and TH in both subpopulations (Figure). The incidences of adverse events (AEs) and serious AEs, including serious AEs of infection, as well as fracture, were similar between treatment groups and consistent with the known safety profile of DMAb.

Table. Baseline Characteristics

	Glucocorticoid-continuing (GC-C)		Glucocorticoid-initiating (GC-I)	
	Risedronate N=252	Denosumab N=253	Risedronate N=145	Denosumab N=145
Sex – n (%)				
Male	67 (26.6)	68 (26.9)	52 (35.9)	52 (35.9)
Female	185 (73.4)	185 (73.1)	93 (64.1)	93 (64.1)
Age (years) – mean (SD)	61.3 (11.1)	61.5 (11.6)	64.4 (10.0)	67.5 (10.1)
Medical conditions of interest – n (%)				
Rheumatoid arthritis	118 (46.8)	96 (37.9)	43 (29.7)	48 (33.1)
Polymyalgia rheumatic	18 (7.1)	20 (7.9)	52 (35.9)	50 (34.5)
Systemic lupus erythematosus	16 (6.3)	15 (5.9)	4 (2.8)	2 (1.4)
Daily prednisone-equivalent dose (mg) – mean (SD)	11.13 (7.69)	12.29 (8.09)	15.61 (10.25)	16.57 (13.01)
25 (OH) vitamin D (ng/mL) – median (Q1, Q3)	28.0 (23.6, 36.3)	29.2 (24.2, 37.6)	28.6 (24.2, 36.4)	28.8 (23.6, 36.0)
BMD T-score – mean (SD)				
Lumbar spine	-1.96 (1.38)	-1.92 (1.39)	-1.06 (1.57)	-0.92 (1.86)
Total hip	-1.56 (0.96)	-1.66 (0.96)	-0.98 (1.07)	-1.14 (1.00)

Figure. BMD Percentage Change From Baseline at Month 12



n=Number of subjects with observed values at baseline and month 12. *p<0.001 compared with RIS.

Conclusions: DMAb significantly increased BMD more than RIS at the spine and hip at 12 months. The overall safety profile was similar between treatment groups. DMAb has the potential to become another treatment option for patients newly initiating or continuing GC who are at risk for fracture.
Acknowledgements: The study was funded by Amgen. C Desborough (Amgen [Europe] GmbH) provided editorial support.
Disclosure of Interest: K. Saag Grant/research support from: Amgen, Merck, Consultant for: Amgen, Merck, Radius, R. B. Wagman Shareholder of: Amgen, Employee of: Amgen, P. Geusens Grant/research support from: Pfizer, Abbott, Lilly, Amgen, MSD, Will, Roche, UCB, BMS, Novartis, J. Adachi Grant/research support from: Amgen, Eli Lilly, Merck, Pfizer, Consultant for: Amgen, Eli Lilly, Merck, International Osteoporosis Foundation, Speakers bureau: Amgen, Eli Lilly, O. Messina Grant/research support from: Amgen, GSK, R. Emkey Speakers bureau: Amgen, R. Chapurlat Grant/research support from: Amgen, Merck, Chugai, Consultant for: Amgen, Eli Lilly, BMS, AbbVie, Pfizer, Chugai, UCB, N. Daizadeh Shareholder of: Amgen, Employee of: Amgen, N. Pannacciulli Shareholder of: Amgen, Employee of: Amgen, W. Lems Grant/research support from: Eli Lilly, Amgen, MSD, Novartis.
DOI: 10.1136/annrheumdis-2017-eular.3164

WEDNESDAY, 14 JUNE 2017

Systematic literature review: the link from science to clinical practice

OP0011 DOES A VERY EARLY THERAPEUTIC INTERVENTION IN VERY EARLY ARTHRITIS / PRE-RHEUMATOID ARTHRITIS PATIENTS PREVENT THE ONSET OF RHEUMATOID ARTHRITIS: A SYSTEMATIC REVIEW AND METANALYSIS

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Background: Recent progress in the understanding of rheumatoid arthritis (RA) pathogenesis leads to growing interest in the concept of pre-RA, a clinical stage in which very early intervention could be more efficacious.
Objectives: To assess the efficacy of very early therapeutic interventions in pre-RA patients, i.e., with either undifferentiated arthritis, or ACPA-positive arthralgia/arthritis (ie, very early RA, VERA), through a systematic literature review (SLR) and meta-analysis (MA).
Methods: The SLR was performed following Cochrane guidelines. The search used "undifferentiated arthritis" or "very early rheumatoid arthritis" (VERA) associated with "therapy" or "treatment", and was limited to randomized controlled trials (RCTs) published in English over the last five years. It was conducted in Pubmed, Embase and Cochrane RCT databases, as well as EULAR and ACR congress abstracts of the last two years. Two independent readers (SH, BH) extracted the following data through a standardized form: study quality, patient status at baseline (either undifferentiated arthritis or VERA), the type of intervention, and disease characteristics over time as well as occurrence of RA.