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Figure 1: Serum urate at different timepoints: Estimates are unadjusted means at week -8 and 0 (dotted line; n=155) and least square means estimates from an ANCOVA model (adjusted for stratification factors, i.e. sex, age category, obesity class as well as the level of the outcome at baseline) for data at 52 weeks (solid lines; n=134). Solid points at week 52 indicate the liraglutide group (n=69) and open points indicate the placebo group (n=65). The error bars indicate SE.

Disclosure of Interests: Kristian Zobbe: None declared, Sabrina Mai Nielsen: None declared, Robin Christensen: None declared, Anders Overgaard: None declared, Henrik Gudbergensen Speakers bureau: Pfizer 2016, Marius Henriksen: None declared, Henning Bliddal Grant/research support from: received research grant fra NOVO Nordic, Consultant of: consultant fee fra NOVO Nordic, Lene Dreyer: None declared, Lisa Stamp: None declared, Filip Krag Knop Shareholder of: Minority shareholder in Antag Therapeutics Aps, Grant/research support from: AstraZeneca, Gubra, Novo Nordisk, Sanofi and Zealand Pharma, Consultant of: Amgen, AstraZeneca, Boehringer Ingelheim, Carmot Therapeutics, Eli Lilly, MSD/Merck, Mundipharma, Novo Nordisk, Sanofi and Zealand Pharma., Speakers bureau: AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, MedImmune, MSD/Merck, Mundipharma, Norgine, Novo Nordisk, Sanofi and Zealand Pharma., Lars Erik Kristensen Consultant of: UCB Pharma (Advisory Board), Sannofi (Advisory Board), Abbvie (Advisory Board), Biogen (Advisory Board), Speakers bureau: AbbVie, Amgen, Biogen, Bristol-Myers Squibb, Celgene, Eli Lilly, Gilead, Forward Pharma, Janssen Pharmaceuticals, MSD, Novartis, Pfizer, and UCB Pharma

DOI: 10.1136/annrheumdis-2020-eular.3088

OP0173

IMMUNOMODULATION CO-THERAPY WITH PEGLOTICASE: DATABASE TRENDS 2014-2019

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Background: Pegloticase is a PEGylated biologic therapy for patients with uncontrolled gout who have not improved on or could not tolerate conventional urate-lowering therapies.¹ All biologics have the ability to engender anti-drug antibodies (ADAs) and it is known that some patients given pegloticase develop ADAs that cause them to stop treatment prior to receiving a complete course of therapy.²⁻³ In other rheumatic autoimmune diseases, DMARDs such as methotrexate or azathioprine are used as standard of care to prevent the development of ADAs to biologics. These DMARDs often allow patients to remain on biologic therapies longer and receive the full therapeutic benefits while minimizing adverse events.⁴ While pegloticase has been used traditionally as monotherapy, recent case series have demonstrated the therapeutic benefit of immunomodulator co-administration, allowing more patients to receive a full course of pegloticase therapy.⁵⁻⁶ Little has been published on how widespread this practice is and whether it has changed over time.

Objectives: To examine medical claims database from 2014-2019 for trends in immunomodulating therapies being co-prescribed with pegloticase.

Methods: An IQVIA claims database (November 2014 to October 2019) representing 1.3 billion claims, covering 30 million patients diagnosed with gout or CKD, was utilized to search for patients who had received pegloticase. Patients who had received pegloticase were classified as having been on an immunomodulating co-therapy if they were prescribed methotrexate or azathioprine within 60 days before or after initiation of their first pegloticase infusion.

Results: We found relatively steady low rates of immunomodulation co-therapy with pegloticase from 2014 through 2018 ranging from 1% in 2016 to 4% in 2018 (Figure 1). In 2019 however, the proportion of pegloticase patients that were co-treated with methotrexate or azathioprine therapy increased to 15%. Most patients were started on immunomodulating therapy 20 days before to 10 days after initiation of pegloticase. Methotrexate was the more frequently used immunomodulation co-therapy as compared to azathioprine.

Figure 1: Proportion of pegloticase patients receiving immunomodulation therapy by year

*Note – any patient starting either methotrexate (MTX) or azathioprine (AZA) within 60 days of their first pegloticase infusion date

Conclusion: We found evidence of a relatively dramatic increasing initiation of immunomodulation therapy with pegloticase beginning soon after a November 2018 presentation of a case series which demonstrated improved response rates of pegloticase when co-administered with methotrexate. These data indicate that clinicians began to more frequently employ a strategy of DMARD co-treatment with pegloticase in 2019 to improve response rates to this important gout medicine.

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Disclosure of Interests: Brian LaMoreaux Shareholder of: Horizon Therapeutics, Employee of: Horizon Therapeutics, Megan Francis-Sedlak Shareholder of: Horizon Therapeutics, Employee of: Horizon Therapeutics, Karl Svensson Shareholder of: Horizon Therapeutics, Employee of: Horizon Therapeutics, Robert Holt Shareholder of: Horizon Therapeutics, Employee of: Horizon Therapeutics

DOI: 10.1136/annrheumdis-2020-eular.3893

OP0174

POLYDATIN PREVENTS CALCIUM PYROPHOSPHATE CRYSTAL-INDUCED ARTHRITIS IN MICE

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Background: Acute calcium pyrophosphate (CPP) crystal-induced inflammation is characterized by the massive release of cytokines and pro-inflammatory mediators and, from a clinical point of view, pain and limited joint function. Contrary to the precipitation of urate crystals that can be prevented through the use of hypouricemic drugs, there is no pharmacological therapy that can prevent the formation of pyrophosphate crystals.

Polydatin (PD), a natural precursor of resveratrol, is a stilbenoid mainly contained in grape juice and bark of *Polygonum cuspidate*. Its antioxidant, anti-inflammatory and immunomodulating properties have been demonstrated in several experimental models. We have recently shown that this compound is able to prevent the inflammatory response to pathogenic crystals in vitro (1).

Objectives: The aim of this study was to assess the anti-inflammatory preventing effect of polydatin in the mouse model of acute crystal-induced arthritis.

Methods: A suspension of sterile CPP crystals (0.3mg/20 µL PBS) have been injected intra-articularly (i.a.) into one ankle joint of Balb/c mice under isoflurane anesthesia. Animals were randomized in 5 groups: 1- CPP injection, 2- CPP + PD, 3- CPP + colchicine (control drug), 4- CPP + vehicle (control. N 1), 5- PBS injection (control N. 2). Polydatin and colchicine were administered by gavage (respectively 40mg/kg and 1mg/kg in 200 µL PBS/EtOH/glucose) at 24, 15 and 1 h before and 1, 6 and 24 h after (prophylactic model) or 1, 6 and 24 h after (therapeutic model) i.a. injection of CPP crystals.

Ankle swelling was measured at different time points using a precision caliper. After 48h (peak of the acute phase) mice were euthanized and blood and ankle

joints were collected for inflammatory cytokine (IL-1 β and KC) determination and histological analysis, respectively.

Results: The mean change in ankle swelling after i.a injection was 0.595 $\pm$ 0.434 mm. Prophylactic treatment with PD and colchicine significantly diminished ankle swelling to 0.175 $\pm$ 0.115 mm and 0.137 $\pm$ 0.100 mm, respectively (Kruskal Wallis p 0.0025; Dunn's post test p < 0.01 CPP vs PD+CPP). The therapeutic administration of PD did not have significant effects on delta swelling (0.468 $\pm$ 0.372 mm - PD vs 0.243 $\pm$ 0.152 mm - colchicine). In mice treated with CPP crystals, histological analysis revealed areas of edema and increased cell infiltrate in articular and periarticular tissues and the presence of reactive lymph-nodes. Tissue necrosis around inflamed tissue has been observed. Treatment with PD importantly reduced cell infiltrate in the prophylactic but not in the therapeutic protocol.

Serum IL-1 β and KC levels, which increased significantly (p <0.05) after 48h from i.a injection, diminished in non significant manner after prophylactic and therapeutic treatment. The gene expression study revealed a reduction of IL-1 β and KC mRNA after PD and colchicine treatment in both groups.

Conclusion: PD can effectively prevent acute inflammatory response to crystals in the mouse model of CPP arthritis. Oral PD prophylactic treatment showed a similar effect of colchicine in reducing ankle swelling and cell infiltrate. However, only colchicine showed to be effective in the therapeutic protocol.

These results raise the possibility that PD might have utility in the prevention of crystal-induced acute attacks in humans.

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Disclosure of Interests: Francesca Oliviero: None declared, Francesca Galupini: None declared, Anna Scanu: None declared, Paola Galozzi: None declared, Vanni Lazzarin: None declared, Paolo Sfriso: None declared, Gianpietro Ravagnan: None declared, Roberta Ramonda Speakers bureau: Novartis, Celgene, Janssen, Pfizer, Abbvie, Lilly, Paolo Spinella: None declared, LEONARDO PUNZI: None declared, Gianmaria Pennelli: None declared, Roberto Luisetto: None declared

DOI: 10.1136/annrheumdis-2020-eular.2124

OP0175

IDENTIFYING PERIPHERAL VASCULAR MONOSODIUM URATE CRYSTAL DEPOSITION WITH DUAL-ENERGY CT: FACT OR FICTION? THE VASCURATE STUDY

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Background: The close relationship between gout and cardiovascular diseases is well established. A growing hypothesis explaining this association would be that monosodium urate (MSU) crystals are deposited within vessel walls. Dual-energy computed tomography (DECT) can identify and quantify MSU crystal deposition in soft tissues. It remains unclear whether vascular spots exhibiting DECT attenuation characteristics of MSU are artefacts or true MSU crystal deposits.

Objectives: The objectives of this study were to determine whether the presence of peripheral vascular MSU crystal deposition identified with DECT is associated with the extent of MSU deposits in joint soft tissues, and if this association persists over time under urate-lowering therapy.

Methods: Patients with a clinical suspicion or established gout diagnosis prospectively underwent DECT for identification and quantification of the MSU crystal burden in their knees and feet. Some of these patients were also enrolled in the GOUT-DECTUS longitudinal study, and thus underwent follow-up DECT scans of their knees and feet at 6, 12 and 24 months. DECT scans were examined for the presence of vascular spots $\geq$ 0.01 cm³ classified as MSU crystal deposits according to the default post-processing settings. Multiple linear regressions adjusting on serum urate levels and gout diagnosis were implemented to determine the association between DECT MSU crystal volume in joint soft tissues, and the presence of vascular MSU deposits. Mixed linear models were used to compare DECT volumes of MSU crystal deposition in soft tissues between vascular MSU positive and negative patients during follow-up.

Results: A total of 169 patients were included, of which 140 had a final diagnosis of gout, including 15 also included in the longitudinal study. Patients were mostly male (78.8%) and were 65.5 $\pm$ 14.6 years old. Among gout patients, disease duration was 9.3 $\pm$ 9.9 years and 56.5% were urate lowering therapy-naïve. A total of 11/29 (37.9%) controls and 40/140 (28.6%) gout patients presented with at least one vascular spot of DECT MSU deposition, with an average volume of 0.02 $\pm$ 0.02 cm³, and all subjects also presented at least one vascular calcification. In the feet, patients positive for vascular DECT MSU crystal deposition had an MSU volume of 3.81 $\pm$ 10.06 cm³ in joint soft tissues, compared with

1.85 $\pm$ 7.72 cm³ for those without vascular MSU deposition (p =0.018). In the knees, patients with vascular MSU deposition had an MSU crystal volume of 6.03 $\pm$ 24.13 cm³ in joint soft tissues, compared with 0.83 $\pm$ 2.88 cm³ for those without vascular evidence of MSU deposition. In the longitudinal subgroup analysis, coefficients of the fixed effects for the presence of vascular MSU deposits on the MSU crystal volume in joint soft tissues was 0.4 (p =0.35) in the feet and 1.21 (p =0.03) in the knees. The presence of vascular DECT MSU deposits was associated with a 3.4-fold increase in MSU crystal volume in knee joint soft tissues throughout follow-up.

Conclusion: This study suggests that some vascular spots identified with DECT as MSU crystal deposition may be real and not artefacts. This correlation remains throughout follow-up in the knees. However, the comparable prevalence of vascular DECT MSU deposits between gout patients and controls, the systematic co-existence of vascular calcifications and the uneven regression under urate-lowering therapy requires further analysis to determine which DECT spots are artefacts and which are not.

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Disclosure of Interests: Tristan Pascart Grant/research support from: Research Grant Horizon Pharma, Consultant of: Novartis, BMS, Sanofi, Pfizer,, Speakers bureau: Novartis, BMS, Paul Carpentier: None declared, Laurène Norberciak: None declared, Julie Legrand: None declared, Eric Houvenagel Speakers bureau: Janssen, Novartis, Fabio Becce: None declared, Jean-François Budzik: None declared

DOI: 10.1136/annrheumdis-2020-eular.4522

Diagnostics and imaging procedures

OP0176

CHRONOLOGICAL ORDER OF DECREASE OF SYNOVITIS, OSTEITIS AND TENOSYNOVITIS IN ARTHRITIS PATIENTS RECEIVING FIRST DMARD-TREATMENT

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Background: During the last decennium advanced imaging modalities have refined our understanding of the tissues involved in RA and have shown that not only joints but also bones and tendons can be inflamed at diagnosis. However, the time-order of decrease of these inflammatory features after initiation of DMARDs is unknown. Whether this differs for ACPA-positive and ACPA-negative patients is also unknown.

Objectives: To achieve better understanding of the time order in which the different inflamed tissues (joint, tendon, bone) respond to DMARD-treatment and whether this differs between ACPA-subgroups.

Methods: 216 consecutive patients with early undifferentiated or rheumatoid arthritis, who received DMARD-treatment, were studied. Unilateral 1.5 Tesla contrast-enhanced MRIs of MCPs, wrists and MTPs were performed at baseline (before treatment) and after 4, 12 and 24 months. MRIs were scored for synovitis, osteitis and tenosynovitis in line with the RAMRIS, in known time-order but blinded for clinical data. Data of 4 serial time-points (three time intervals) were studied with autoregressive cross-lagged models. These models evaluated the influence of two time patterns in one model: 1) a simultaneous pattern ("extra change in one inflammatory feature was associated with extra change in another feature") and 2) a subsequent pattern ("change in one inflammatory feature preceded change in another feature"). All analyses were repeated stratified for ACPA-status (anti-CCP2).

Results: In all patients, all combinations of inflammatory features showed significant simultaneous decrease in all time intervals (0 - 4 / 4 - 12/12 - 24 months; all p <0.05). In addition to simultaneous changes there were also time orders identified: synovitis change between 0 - 4 months preceded tenosynovitis change between 4 - 12 months (p =0.03) and synovitis change between 4 - 12 months preceded tenosynovitis change between months 12 - 24 months (p =0.02).

When considering ACPA-negative and ACPA-positive patients separately, similar results were obtained. In addition, in ACPA-positive patients, synovitis change between 4 - 12 months preceded osteitis change at 12 - 24 months (p = 0.002); this was significantly different from ACPA-negative patients (p <0.001).

Conclusion: This study increased the understanding of the response to treatment on tissue level. In addition to simultaneous decrease of synovitis, osteitis and tenosynovitis, also time orders of inflammation decrease were identified.