Disclosure of Interests: Mihaela Gamala: None declared, Johannes W. G. Jacobs Grant/research support from: Roche, Consultant for: Roche, Suzanne Linn-Rasker: None declared, Maarten Nix: None declared, Ben Heggelman: None declared, Pieter Pasker: None declared, Jacob M. van Laar Grant/research support from: Genentech, Consultant for: F. Hoffmann-La Roche, Ruth Klaassen: None declared

DOI: 10.1136/annrheumdis-2019-eular.509

OP0051

DEVELOPMENT OF A MULTIVARIABLE IMPROVEMENT MEASURE FOR GOUT

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Background: Inflammatory rheumatic diseases are generally multifaceted disorders and the complex pathology underlying these conditions makes it difficult to assess patient status and the efficacy of therapy with a single outcome measure. This has prompted the development of composite measures for many rheumatic diseases. Gout is also a multifactorial inflammatory disease in which patients experience a wide range of signs and symptoms, including intermittent and persistent pain and inflammatory arthritis, tophi and disability. Most assessments of gout and response to urate-lowering therapy (ULT) have focused primarily on the ability to lower serum urate and decrease the frequency of flares. Recognition that assessment of ULT and other treatments for gout could be facilitated by endpoints that more closely reflect the multidimensional impact of the disease has prompted an interest in developing composite measures, although there is no consensus on the most appropriate composite measure to employ.

Objectives: To develop an evidence-based gout multivariable improvement measure (GMIM) that captures the spectrum of gout manifestations and is sensitive to change.

Methods: Databases from patients with chronic refractory gout who participated in two randomized 6 month clinical trials (RCTs) of pegloticase were reviewed¹. Sub-sets who had persistent urate lowering (responders) to biweekly pegloticase (n=36) and those who had only transient urate lowering (non-responders, n=49) were identified and compared to those who received placebo (n=43). Initially individual patients were assessed for achievement of previously reported criteria for remission²: serum urate <6 mg/dL, absence of tophi and flares, patient global assessment, and pain (each <2 on a 10-point visual analog scale). A repeated measures mixed effects model controlling for repeated observations with backward elimination using data from these patients was employed to determine the model components that best correlated with time to maximum benefit³. This analysis resulted in the addition of swollen and tender joints to the outcome measure. In order to assess the degree of improvement, each subject was scored based upon a serum urate <6 mg/dL and 20, 50 or 70% improvement in ≥4 of the 6 clinical evaluations and termed GMIM20, 50, 70.

Results: GMIM was able to capture gradation of change in the treated populations and also distinguish responses in those with persistent versus those with transient urate lowering and subjects treated with placebo (Figure 1). At 3 and 6 months, achievement of GMIM20, 50 and 70 in persistent responders occurred significantly more often vs placebo and versus non-responders without persistent urate lowering. Sensitivity analysis indicated that flares contributed minimally to the model.

Figure 1: Percentage of Subjects Meeting GMIM Response Criteria

Conclusion: GMIM effectively captures changes in disease severity in response to treatment in patients with advanced gout treated with pegloticase. GMIM20,50,70 may serve as an evidence-based tool for assessment of the quality of response to therapies in subjects with gout in medical practice or in clinical trials.

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Disclosure of Interests: Naomi Schlesinger Consultant for: Astra Zeneca, Novartis, Horizon Pharma, N. Lawrence Edwards Consultant for: Horizon Pharma, Astra Zeneca, Selecta Biosciences, Anthony Yeo Employee of: Horizon Pharma, Peter Lipsky Consultant for: Consulting fees from Horizon Pharma

DOI: 10.1136/annrheumdis-2019-eular.2904

OP0052

FAILURE TO REACH SERUM URATE TARGET IS ASSOCIATED WITH ELEVATED MORTALITY IN GOUT

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Background: Gout is associated with an increased risk of cardiovascular events and death. It has been shown that both overall and risk of death are associated with increasing gout severity, as reflected by the number of tophi. It remains to be proven whether better control of gout through lowering of serum uric acid (sUA) confers a survival advantage.

Objectives: To determine the impact of achieving sUA less than 6 mg/dl (vs greater) on mortality risk among gout patients.

Methods: Analysis of data from a prospective follow-up cohort (1992 to 2017) of patients attending a gout clinic (85% of patients with microscope or ultrasound diagnosis) and with at least one follow-up visit. Mortality was confirmed from medical records, patients' families, or local death registries if needed. sUA levels were monitored during follow-up and the average sUA until sUA was stable was used as the primary exposure dichotomized as < 6 mg/dl (versus ≥ 6 mg/dl). Descriptive variables and potential confounders included: age, gender, body mass index, previous treatment with urate-lowering drugs (ULDs), number of joints affected at entry, presence of subcutaneous tophi, radiographic evidence of articular damage, number of gout flares in the year preceding evaluation, previous diagnosis of cardiovascular (CV) disease, loop diuretic use, alcohol intake, diabetes, hypertension, hyperlipidemia, and renal function impairment. In addition, the Kaiser Permanente stratification of comorbidity was further used to risk stratify patients from low to high risk of death. Univariate and multivariate Cox proportional hazards models were used to determine mortality risks expressed a hazard ratios (HR) and 95% Confidence Intervals (CI).

Results: The study cohort included 1,193 patients (92% men, mean age 60, 6.8 years disease duration, with an average of 3-4 flares in the previous year). Mean follow-up was 48 (median 30, IQR 12-66), with 4,830 patient-year observation. Mean sUA at baseline was 9.1 mg/dl and 16.3% of the patients maintained sUA levels ≥ 6 mg/dl despite treatment. A total of 158 deaths occurred (13% overall mortality), with loss to follow-up in 286 cases (24%). Overall crude mortality rate was 32.7 per 1,000 patient-years, (95% CI: 28.0-38.2) and was significantly higher for patients with sUA ≥ 6 mg/dl, 80.9 per 1,000 person-years (95% CI 59.4-110.3) compared to patients with sUA < 6 mg/dl, 25.7 per 1,000 person-years (95% CI: 21.3-30.9). With adjustment for age, sex, previous CV events, and baseline sUA concentration, a sUA ≥ 6 mg/dl was associated with a HR of 2.39 (1.64 - 3.50).

Conclusion: Failure to reach a target sUA level of 6 mg/dl is an independent predictor of mortality in gout patients. Control of gout with achievement of sUA target < 6 mg/dl should be considered in order to improve patient survival.

Disclosure of Interests: Fernando Perez-Ruiz Grant/research support from: Cruces Rheumatology Association, Consultant for: Grunenthal, Menarini, Horizon, Speakers bureau: Menarini, Grunenthal; Spanish foundation for rheumatology, Pascal Richette Consultant for: Grunenthal, Horizon, Speakers bureau: AstraZeneca, Grunenthal, Austin Stack Grant/research support from: Menarini, Consultant for: Grunenthal, AstraZeneca, Speakers bureau: Menarini, Grunenthal, Ravi Karra Employee of: Grunenthal, María Jesús García de Yébenes: None declared, Loreto Carmona Grant/research support from: Abbvie, Actelion, Astellas, BMS, Eisay, Gebro Pharma, Grünenthal, Leo Pharma, Lilly, MSD, Novartis, Pfizer, Roche, Sanofi-Aventis and UCB Pharma, Paid instructor for: Novartis

DOI: 10.1136/annrheumdis-2019-eular.5905

OP0053

CERAMIDES AND DIHYDROCERAMIDES LEVELS ARE ASSOCIATED WITH THE INFLAMMATORY RESPONSE IN A MURINE MODEL OF GOUT

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Background: The metabolic syndrome is strongly associated with gout and hyperuricemia in man. Patients with gout commonly report acute flares after eating particular foods and it is suspected that metabolic changes, apart from serum urate levels, influence the triggering of the inflammatory response to MSU crystals.

Objectives: By studying the metabolic changes that impact on the response to MSU crystals in a murine model of gout, we hope to identify the dietary effect on metabolites that are associated with the inflammatory response to MSU crystals.

Methods: Male mice (C57BL/6) were fed either a normal diet (ND) or high fat diet HFD (DIO D12492) for >6 weeks. During the last 4 weeks of feeding, half the mice in each group were treated with antibiotics (Enrofloxacin 0.25% + co-amoxicillin) to induce a germ-free state. At day 0, mice were injected i-p with 1 mg of MSU crystals. Mice were sacrificed 6h after i-p injection. Serum, plasma and peritoneal exudate samples were collected at sacrifice and plasma obtained 3 weeks before sacrifice. Untargeted and targeted liquid chromatography – mass spectrometry based-metabolomics approach was performed on serum and plasma samples. IL1 and IL6 were measured in serum and peritoneal exudates by ELISA. Animal experimental authorization was obtained for these experiments.

Results: Mice fed a HFD had a greater serum and peritoneal IL6 response to MSU. In an untargeted analysis, multiple metabolic alterations were observed related to diet. Targeted analyses of sphingolipids were performed. Both diet and inflammation (MSU injection) altered plasma sphingolipid levels. No effect of antibiotics was observed. MSU injection induced marked changes in the sphingolipid profile (38.2% of explained variance), while diet had a lesser effect (16.2% of explained variance). Mice fed an HFD had significantly higher serum IL6 before and peritoneal IL6 levels after MSU injection than mice fed a ND. DhCer C16:0 and Cer C16:0 levels decreased significantly after MSU injection. Pre-MSU levels of DhCer C16:0 and Cer C16:0 showed significantly negative correlations with IL6p levels after i-p injection in HFD animals.

Conclusion: The sphingolipid profile was significantly changed by diet and inflammation. In mice given a HFD, the levels of particular ceramides were significantly correlated with subsequent inflammatory response as assessed by IL6 secretion, suggesting that they may play a role in modulating the inflammatory response to MSU. These same ceramides and their derivatives have been linked to susceptibility to diabetes and cardiovascular diseases^{1,2}. Further investigation of these sphingolipids in gout in man is warranted.

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Disclosure of Interests: Alexander So Consultant for: SOBI, Grunenthal, Speakers bureau: Grunenthal, Florence Mehl: None declared, Nicola Harris: None declared, Veronique Chobaz: None declared, Hector Gallart-Ayala: None declared

DOI: 10.1136/annrheumdis-2019-eular.6681

OP0054 OCCUPATIONAL EXPOSURE TO INORGANIC DUST – A NOVEL RISK FACTOR FOR INCIDENT GOUT?

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Background: Hyperuricemia and factors contributing to it are strong risk factors for gout but it is still unexplained why only some individuals with hyperuricemia develop gout. Additional risk factors for gout could be genetic or related to comorbidity, lifestyle or occupation. Occupational exposure to inorganic dust has previously been linked to an increased occurrence of inflammatory rheumatic diseases such as rheumatoid arthritis and could possibly increase the risk of gout.

Objectives: To evaluate if occupational exposure to inorganic dust increases the risk of incident gout.

Methods: Gout was defined as having at least one ICD-10 code for gout (M10 or M14.0) in the population based health care database of the Western Swedish Health Care Region (VEGA), during the years 2006-2012, without any gout diagnosis during at least 6 years previously. Individuals with gout that were employed in the 5-year period prior to first diagnosis were included for analysis. Population controls without gout were identified in the census register by Statistics Sweden, matching up to 5 controls per case on the basis of age, sex and place of residence, excluding controls that were not employed during the predictor period. Data on occupation (coded by the ISCO-88 standard) for the 5 years prior to inclusion were collected from official registries and were used to assign exposure status using a job exposure matrix for inorganic dust previously developed.^[1] Data on predefined comorbidities (psoriasis, renal disease, alcohol abuse, obesity and diuretic treatment) considered to be possibly relevant confounders for the analyses were collected from VEGA, defined by ICD-10 codes. Alcohol abuse and obesity were found to be related both to gout and exposure to inorganic dusts and

were therefore adjusted for in multivariate analyses. The effect of exposure to inorganic dust on risk of gout was described with odds ratios, calculated using conditional logistic regression, for the whole population and stratified by sex.

Results: 6120 gout cases and 25074 controls were included. Frequencies of exposures (n (%)) and odds ratios (OR (95% conf. int.)) for association of risk factors with incident gout are shown in the table below.

		Exposed to inorganic dust	Alcohol abuse	Obesity
Whole population	Gout cases, n=6120	1836 (30)	299 (5)	671 (11)
	Controls, n=25074	7074 (28)	538 (2)	821 (3)
	OR univariable	1.10 (1.04 to 1.17)	2.37 (2.04 to 2.74)	3.81 (3.42 to 4.26)
	OR multivariable*	1.07 (0.99 to 1.14)	2.26 (1.94 to 2.62)	3.75 (3.36 to 4.19)
Men	Gout cases, n=4751	1615 (34)	267 (6)	489 (10)
	Population controls, n=19339	6343 (33)	471 (2)	576 (3)
	OR univariable	1.07 (1.00 to 1.15)	2.42 (2.07 to 2.82)	3.93 (3.45 to 4.48)
	OR multivariable*	1.03 (0.97 to 1.11)	2.29 (1.95 to 2.69)	3.85 (3.38 to 4.39)
Women	Gout cases, n=1369	221 (16)	32 (2)	182 (13)
	Population controls, n=5735	731 (13)	67 (1)	245 (4)
	OR univariable	1.33 (1.12 to 1.57)	2.02 (1.31 to 3.11)	3.53 (2.87 to 4.34)
	OR multivariable*	1.27 (1.07 to 1.51)	2.03 (1.31 to 3.14)	3.50 (2.85 to 4.31)

*includes inorganic dust, alcohol abuse and obesity as covariates.

Conclusion: As expected, previously known risk factors for gout such as obesity and alcoholism were strongly associated with incident gout. In univariate analyses, exposure to inorganic dust was also associated with gout. After adjusting for alcohol abuse and obesity, the relationship was attenuated in men but remained in women, providing evidence that occupational exposure to inorganic dust might be a previously unknown risk factor for gout.

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Disclosure of Interests: Valgerdur Sigurdardottir: None declared, Anna Svärd: None declared, Lennart T.H. Jacobsson Consultant for: LJ has received lecture and consulting fees from Pfizer, Abbvie, Novartis, Eli-Lilly and Janssen, Linus Schiöler: None declared, Kjell Torén: None declared, Mats Dehlin: None declared
DOI: 10.1136/annrheumdis-2019-eular.804

WEDNESDAY, 12 JUNE 2019

JIA: From new horizons of treatment to perspectives of current ones

OP0055 EFFICACY OF CANAKINUMAB, ON A REDUCED DOSE OR A PROLONGED DOSE INTERVAL WITHOUT CONCOMITANT CORTICOSTEROIDS AND METHOTREXATE, IN PATIENTS WITH SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS

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Background: Canakinumab (CAN), a selective, human anti-IL-1β mAb, has shown sustained therapeutic effect along with corticosteroid (CS) dose reduction/discontinuation in patients (pts) with systemic juvenile idiopathic arthritis (SJIA), in a long-term extension study (NCT00891046).¹

Objectives: To evaluate the efficacy and safety of 2 different CAN tapering regimens in SJIA pts who were in clinical remission (NCT02296424).