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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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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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-1 β 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).

Methods: This Phase 3b/4 study had 2 parts. Of 182 enrolled pts, 166 pts with inactive disease (ID) (cohort 1; 68pts)¹ and CAN-naïve pts (cohort 2; 98pts) were administered subcutaneous CAN 4mg/kg q4w in Part I. Per protocol titration off CS and/or methotrexate (MTX) was attempted during Part I. Eligible pts (ID for 24 weeks[wks] and being CS- and MTX-free for at least 4 wks) advanced to Part II wherein, pts were randomised to either a 3-step CAN dose reduction (2mg/kg/q4w, followed by tapering to 1 mg/kg/q4w and then discontinuation) or dose interval prolongation (4mg/kg q8w, followed by tapering to 4mg/kg/q12w and then discontinuation); pts advanced to the next tapering step if ID was maintained for 24 wks. Adapted American College of Rheumatology (ACR) paediatric criteria, its individual components and Juvenile Arthritis Disease Activity Score (JADAS) were assessed.

Results: In total, 75 pts were randomised to a dose reduction (n=38) or dose interval prolongation (n=37) CAN tapering regimen in part II. The pts who maintained ID for 24 wks exceeded the predefined threshold of 40% for the reduced CAN dose arm (71%) and prolonged dose interval (84%) treatment arm of Step 1 (primary endpoint). A total of 68.4% (26/38) and 81.1% (30/37) pts in the dose reduction and interval prolongation arms, respectively were successful in Step 2; 33% (25/75) of pts successfully discontinued CAN and maintained ID for 24 wks. ID, ACR 90/100 and JADAS 27 C-reactive protein (CRP) scores are summarised in the table. Adverse events (AEs) and serious AEs observed within the 2 cohorts and across Parts I and II were similar. The most frequent AEs were common infections (nasopharyngitis, upper respiratory tract infection, pharyngitis) followed by SJIA-related events (rash, pyrexia and arthralgia).

Table 1. Efficacy responses of Part I over 24 Wks

	Cohort 1 N=68	Cohort 2 N=98
Inactive disease, n (%)		
BL	56 (82.4)	0.0
Wk 4	61 (89.7)	45 (45.9)
Wk 24	67 (98.5)	67 (68.4)
Median JADAS27-CRP, range (min, max)		
BL	1.1 (0.0, 35.5)	22.8 (4.9, 48.0)
Wk 4	5.05 (0.0, 12.97)	2.6 (0.0, 41.7)
Wk 24	1.0 (0.0, 27.8)	2.0 (0.0, 31.5)
ACR 90, n (%)		
BL	17 (25)	
Wk 4	0 (0.0)	13 (13.3)
Wk 24	13 (19.1)	15 (15.3)
ACR 100, n (%)		
BL	38 (55.9)	
Wk 4	2 (2.9)	31 (31.6)
Wk 24	34 (50)	44 (44.9)

N, total number of patients; n, number of patients

Conclusion: SJIA pts with ID for 24 wks on CAN monotherapy can successfully taper CAN by either reducing the dose or prolonging the dosing interval. However, only a minority of pts overall successfully discontinued CAN treatment and maintained ID for 24 wks. The safety profile was similar and consistent with other CAN SJIA studies. No new safety signals were identified.

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OP0056

MAINTENANCE OF CLINICAL RESPONSE IN INDIVIDUAL CHILDREN WITH JUVENILE IDIOPATHIC ARTHRITIS TREATED WITH SUBCUTANEOUS ABATACEPT

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Background: The efficacy of SC abatacept (ABA) in patients (pts) with polyarticular-course juvenile idiopathic arthritis (pJIA) was shown in a 2-year (yr), Phase III, open-label international study (NCT01844518).¹ However, it is unknown whether each individual pt within a treatment group consistently achieves the same efficacy endpoint at all time points.

Objectives: To investigate whether ABA efficacy is maintained by individual pts with pJIA over time.

Methods: In this subgroup analysis, pts in two age cohorts (2–5 yrs and 6–17 yrs) who achieved clinical response to weekly SC ABA (10 to <25 kg [50 mg], 25 to <50 kg [87.5 mg], ≥50 kg [125 mg]) at Day 113 (time point of primary pharmacokinetics endpoint¹) were followed for 2 yrs. Stringent efficacy outcomes selected for analysis included JIA-ACR70, JIA-ACR100, Juvenile Arthritis Disease Activity Score 71 (JADAS71) minimal disease activity (MDA; ≤3.8) and JADAS71 inactive disease (ID; ≤1) rates. Prognostic factors for sustained response were investigated using logistic regression.

Results: A total of 219 pts entered the study (46 [21.0%] 2–5 yrs; 173 [79.0%] 6–17 yrs) and a subgroup of these pts achieved a clinical response at Day 113 (Table). Most pts who achieved JIA-ACR70, JIA-ACR100, JADAS71 MDA and JADAS71 ID at Day 113 sustained their response at Day 393 and at Days 393 and 645 in the 2–5-yr and 6–17-yr cohorts (Figure). Across cohorts, more than 75% and 60% of pts maintained a JIA-ACR 70 and JADAS71 MDA response through Day 645, respectively. Prior biologic (b)DMARD use was an important prognostic factor. In pts aged 6–17 yrs, sustained JIA-ACR70 response rate at Days 393 and 645 was 81% (57/70) in pts who did not have prior bDMARDs vs 57% (12/21) in pts who had prior bDMARDs (p=0.0715); sustained JADAS71 MDA response rate was 71% (37/52) vs 37% (7/19; p=0.0320). Prognostic factors for JIA-ACR100 response and JADAS71 ID in pts aged 6–17 yrs and for all outcomes in pts aged 2–5 yrs could not be determined due to low pt numbers.

Conclusion: The majority of individuals with pJIA who achieved stringent efficacy endpoints with weekly SC abatacept by Day 113 sustained that clinical endpoint over time. Prior bDMARD use may be a prognostic factor for sustained response over 2 yrs.

Table. Proportion of pts who achieved a clinical response at Day 113

Endpoint	Pts with response at Day 113	
	2–5 yrs (n=46)	6–17 yrs (n=173)
JIA-ACR70	34 (74)	91 (53)
JIA-ACR100	19 (41)	25 (15)
JADAS71 MDA	28 (61)	71 (41)
JADAS71 ID	17 (37)	28 (16)

Data are expressed as n (%)

ID=inactive disease; JADAS71=Juvenile Arthritis Disease Activity Score 71; MDA=Minimal disease activity; p=patient; yr=year

Figure. Proportion of responders at Day 113 with sustained clinical response at Day 393 and at Days 393 and 645 in A) cohort aged 2–5 yrs and B) cohort aged 6–17 yrs