Disclosure of Interests: None declared
DOI: 10.1136/annrheumdis-2019-eular.4039

OP0049

FACTORS ASSOCIATED WITH EARLY FLARES WHEN INITIATING URATE LOWERING THERAPIES. POST HOC ANALYSIS OF CLEAR 1,2 AND CRYSTAL TRIALS

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Background: Initiation of urate lowering therapies (ULT) in patients with gout can trigger flares which could contribute to poor treatment adherence. The EULAR guidelines recommend a prophylactic treatment with colchicine or low dose NSAIDs for up to 6 months. However, long term treatment with either NSAIDs or colchicine can be poorly tolerated or contra-indicated. Thus, identification of risk factors for flares to identify patients who would benefit more from a prophylactic treatment could improve patients care.

Objectives: To investigate the influence of patient and treatment related factors on the occurrence of flares 1 month after the initiation of ULT.

Methods: Data are from n=1018 patients (mean age 52.0 (SD 11.1) years; 95.2% male) not responding to allopurinol or febuxostat monotherapy and who received lesinurad (200 mg or 400 mg) in the CLEAR and CRYSTAL trials. Patients were prescribed colchicine (84%) or NSAIDs (12.9%) as prophylactic treatment. Data from 3 trials were pooled and the following covariates were considered in the main analysis using a Generalized Estimation Equation (GEE) model: age, gender, serum uric acid (SUA) levels, baseline body mass index, renal function, and presence of tophus, type of gout flare prophylaxis, triglycerides, comorbidities (smoking, tobacco, diabetes, hypertension, hyperlipidemia) antihypertensive and lipid lowering medications at baseline and newly started and change in SUA levels. A multivariate analysis was conducted using the occurrence of flares as response measured from baseline until month 1

Results: In the multivariate analysis, tophus at baseline and gender (female) were both associated with an increased risk of early flares: OR=2.7 (95% CI: 1.7-4.2) and OR=1.8 (95% CI: 1.0-3.4), respectively, whereas hyperlipidemia and hypertension were associated with a decreased risk of flares: OR=0.64 (95% CI: 0.45-0.91) and OR= 0.62 (95% CI: 0.39-0.99). There was a trend toward a reduced risk of flares with colchicine versus NSAIDs: OR=0.71 (95% CI: 0.47-1.05). Neither the duration of gout nor the change in SUA levels modified the risk of flares.

Conclusion: This analysis shows that gender (female) and tophus are independent risk factors of early flares when initiating ULT, and suggests that colchicine might be more effective than low dose NSAIDs as prophylactic treatment.

Disclosure of Interests: Pascal Richette Consultant for: Grunenthal, Horizon, Speakers bureau: AstraZeneca, Grunenthal, Fernando Perez-Ruiz Grant/research support from: Cruces Rheumatology Association, Consultant for: Grunenthal, Menarini, Horizon, Speakers bureau: Menarini, Grunenthal; Spanish foundation for rheumatology, Ravi Karra Employee of: Grunenthal, Augustin Latourte: None declared, Imane Wild Employee of: Grunenthal, Prashanth Kandaswamy Employee of: Grunenthal, Heiko Hagedorn Employee of: Grunenthal, Thomas Bardin Consultant for: AstraZeneca, Grunenthal, Horizon, Novartis, Speakers bureau: Astella, AstraZeneca, Grunenthal.

DOI: 10.1136/annrheumdis-2019-eular.4679

OP0050

ADDITIVE VALUE AND DIAGNOSTIC ACCURACY OF DUAL-ENERGY CT FOR THE DIAGNOSIS OF GOUT: A PROSPECTIVE STUDY IN SUBJECTS WITH UNCLASSIFIED MONO OR OLIGOARTHRITIS

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Background: The latest diagnostic technique to visualize monosodium uric acid (MSU) depositions is Dual Energy CT scan (DECT).¹

Objectives: To assess the additive value and accuracy of DECT in diagnosing gout in a prospective study in subjects with unclassified arthritis.

Methods: We included 100 consecutive patients with acute unclassified mono or oligo arthritis who presented to the outpatient clinic of the Department of Rheumatology of Meander Medical Centre, Amersfoort, the Netherlands, ClinicalTrials.

gov NCT03038386. Eleven patients dropped out, see Figure. Patients underwent aspiration of the arthritic joint (see Table) and a DECT scan of hands and wrists, knees, ankles and feet bilaterally. The 2015 EULAR/ACR gout classification criteria were used to score the subjects, with and without DECT result, to determine the additive value of DECT. Sensitivity and specificity of DECT for diagnosing gout were calculated separately for at the joint and at individual persons' level, using as reference standards microscopy of synovial fluid (SF) and the gout classification criteria.

Results: For demographic and clinical characteristics of the patients see Table 1, and for study data and outcomes see Figure and Table 2. Sixty-eight of 89 patients (76.4%) fulfilled the 2015 EULAR/ACR criteria for gout. Of the 98 patients with SF aspiration, 55 (56%) were positive for MSU; of these, 89 subjects underwent DECT, of whom 38 had a negative microscopy result. Of these 38 subjects, 14 (37%) met the gout classification criteria only after a positive DECT result.

Conclusion: Our findings suggested that DECT could have an additive value to clinical algorithms in subjects with undifferentiated arthritis when microscopy of SF fails to demonstrate the presence of MSU crystals.

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Table 1. The characteristics of the patients (n=89) in the analysis

	Patients MSU positive (n=51)	Patients MSU negative (n=38)
Age, years, mean (SD)	60 (16)	64 (12)
Gender, N (%)		
Male	44 (86.3)	38 (73.7)
Arthritic joint aspirated (N,%)		
MTP1	32 (66.7)	8 (21.1)
Other joints	19 (33.3)	31 (78.9)
Period between 1 st arthritis attack and baseline visit in months, median (IQR)*	12 (0.9-48)	5.5 (0.2-36)
Serum uric acid (μmol/L) mean (SD)	499 (88)	411 (101)

* according to patient

Table 2. Diagnostic accuracy of DECT

DECT evaluation method	Reference standard	TP	FP	FN	TN	Sensitivity (95%CI)	Specificity (95% CI)	Diagnostic accuracy (95%CI)
joint/localisation based patient based	MSU	28	13	23	25	0.55 (0.40- 0.69)	0.66 (0.49 - 0.80)	0.60 (0.49- 0.70)
joint/localisation based patient based	MSU	39	20	12	18	0.77 (0.63- 0.87)	0.47 (0.31- 0.64)	0.64 (0.53- 0.74)
joint/localisation based patient based	EULAR/ ACR 2015	41	0	27	21	0.60 (0.48 - 0.72)	1 (0.84-1)	0.70 (0.59 - 0.79)
joint/localisation based patient based	EULAR/ ACR 2015	56	3	12	18	0.82 (0.71- 0.91)	0.86 (0.64- 0.97)	0.83 (0.74- 0.90)
joint/localisation based patient based	MSU	11	7	9	12	0.55 (0.32- 0.76)	0.63 (0.38- 0.84)	0.59 (0.42- 0.74)
joint/localisation based patient based	MSU	16	10	4	9	0.80 (0.56- 0.94)	0.47 (0.24- 0.70)	0.64 (0.46- 0.78)
joint/localisation based patient based	EULAR/ ACR 2015	18	0	11	10	0.60 (0.42- 0.79)	1 (0.69-1)	0.72 (0.55- 0.85)
joint/localisation based patient based	EULAR/ ACR 2015	25	1	4	9	0.86 (0.68- 0.96)	0.90 (0.56- 0.99)	0.87 (0.73- 0.96)

joint-/localisation-based evaluation, person based evaluation: imaging results positive for gout if green pixilation were observed at the index joint, at the index joint and/or in other locations, respectively.

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, Pietermel Pasker: None declared, Jacob M. van Laar Grant/research support from: Genentech, Consultant for: F. Hoffmann-La Roche, Ruth Klaasen: 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.