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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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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.

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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.