Serum Urate as a Soluble Biomarker in Chronic Gout—Evidence that Serum Urate Fulfills the OMERACT Validation Criteria for Soluble Biomarkers

Lisa K. Stamp, FRACP, PhD,*,† Xiaoyu Zhu,*
Nicola Dalbeth, FRACP, MD,‡ Sarah Jordan, FRACP,†
N. Lawrence Edwards,§ and William Taylor, FRACP, PhD¶

Objectives: To determine whether serum urate (SU) fulfills the Outcome measures in Rheumatology (OMERACT) soluble biomarker criteria.

Methods: The OMERACT soluble biomarker criteria were adapted for use in chronic gout. Potential outcome measures for use in chronic gout were identified. The literature was reviewed to determine which of the potential outcome measures were appropriate and whether there was evidence within the current literature to fulfill the OMERACT biomarker criteria.

Results: The assay for measurement of SU is reliable, internationally standardized, and readily accessible for use in clinical practice. The effects of sources of variability, including age, sex, ethnicity, circadian rhythms, body mass index, renal/hepatic function, and fasting, are well documented. Tophus regression was identified as appropriate structural outcome measure; however, given that not all patients have clinically apparent tophi, the number of gout flares is also identified as a key outcome measure.

Conclusions: Serum urate fulfills all the OMERACT biomarker criteria with the exception of its effects on outcome measures. Further analysis of existing and new data sets to determine whether a reduction in SU predicts a reduction in gout flares, the number/size of tophi, and patient reported outcomes using validated measures for these outcomes are required.

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Gout is the most common form of inflammatory arthritis in men over 40 years of age. The primary biochemical abnormality in gout is an increase in serum urate (SU) concentration. When supersaturation concentrations are reached, 6.8 mg/dL (0.41 mmol/L) at 37°C, monosodium urate (MSU) crystals may form and can deposit in joints and periarticular tissues. Once deposited, MSU crystals cause damage through tophus formation and chronic gouty synovitis. Painful attacks of gout are caused by an acute inflammatory response to MSU crystals within joints. Inadequately treated gout leads to recurrent acute attacks, formation of tophi, and joint damage.

The key to successful management of gout is adequate and sustained reduction of SU. SU is thus regarded as a critical outcome measure in the management of gout and in gout clinical trials. Both the British Society for Rheumatology and the European League against Rheumatism have published guidelines for the management of gout, which include a target SU concentration 5 mg/dL (0.30 mmol/L) and 6 mg/dL (0.36 mmol/L), respectively (1,2).

The Outcome measures in Rheumatology (OMERACT) gout special interest group has highlighted the lack of validated clinical outcome measures for both acute and chronic gout studies (3). Consensus exercises identified

*Department of Medicine, University of Otago, Christchurch, New Zealand.
†Department of Rheumatology, Immunology, and Allergy Christchurch Hospital, Christchurch, New Zealand.
‡Department of Medicine, University of Auckland, Auckland, New Zealand.
§Department of Medicine, University of Florida, Gainesville, FL.
¶University of Otago, Wellington, New Zealand.

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Address reprint requests to Lisa K. Stamp, FRACP, PhD, Department of Medicine, University of Otago, Christchurch, P.O. Box 4345, Christchurch 8140, New Zealand. E-mail: lisa.stamp@cdhb.govt.nz.

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SU as an important outcome measure in chronic gout studies with the highest median rating (4). At the recent OMERACT 10 meeting SU was accepted has having fulfilled the OMERACT filter. However, as an outcome measure, SU is a surrogate biomarker for key clinical outcomes that are of importance to both patients and their physicians.

OMERACT has developed a schema for validation of soluble biomarkers in rheumatoid arthritis (RA), psoriatic arthritis (PsA), and spondyloarthritis (SpA) (5). While not specifically developed for gout, the key essential criteria (Appendix 1) provide the basis for validating SU as a soluble biomarker in chronic gout. While the biomarker criteria for RA, PsA, and SpA focus on the structural endpoint of radiographic change, the relationship between the SU and key clinical and patient-centered outcomes is more relevant in gout.

A literature review was undertaken to collate the published evidence that demonstrates the validity of SU as a soluble biomarker according OMERACT filter in chronic gout.

METHODS

OMERACT Soluble Biomarker Criteria

The essential criteria from the OMERACT soluble biomarker criteria were adapted for use in chronic gout as follows.

Truth and Discrimination

1. The assay for measurement of SU is reproducible according to reliability analysis.
2. The effects of sources of variability on SU concentrations in appropriate controls are known for the following core variables: age, sex, ethnicity, circadian rhythms, body mass index (BMI), renal/hepatic function, fasting/nonfasting, medications, and cardiovascular disease.
3. SU demonstrates independent association with clinical and patient-centered endpoints. The key clinical/patient-centered endpoints in chronic gout are as follows: number of gout flares, tophus regression, dissolution of crystals, radiographic damage, and patient function and quality of life (QOL) (4).

Feasibility

1. The assay for measurement of SU is internationally standardized (availability of reference standards) and is readily accessible if used for clinical practice.
2. Stability of SU at room temperature, in frozen specimens, after repeat freeze/thaw cycles, and after long-term storage has been documented.

Literature Search

We conducted a systematic literature review to determine if SU fulfilled the modified OMERACT soluble biomarker criteria outlined above. A MEDLINE literature search was undertaken through to March 2010. The search strategy and keywords for each of the criteria are outlined in Table 1. All articles were reviewed for additional references.

Study Eligibility, Selection, and Data Abstraction

All studies examining the relationship between SU and the examined variables and outcome measures were eligible for inclusion. No geographic restrictions were applied. All data were extracted by 2 investigators (X.Z. and S.J.) and validated by a third investigator (L.K.S.). A set form was used to obtain information on study characteristics, participants, and relationship between SU and the variables/outcome measures.

Analysis

All SU concentrations were converted to mmol/L and mg/dL using a conversion factor of 1 mg/dL = 59.48 μmol/L. Results are reported as mean SU $\pm$ standard deviation and odds ratios of events (OR) (95% confidence intervals) as appropriate.

RESULTS AND DISCUSSION

The numbers of studies assessed and included in the literature review are outlined in Figure 1. For each study, data relating to relationship between SU and the soluble biomarker criterion were obtained and are outlined below.

Truth and Discrimination

1. The Assay for Measurement of SU Is Reproducible According to Reliability Analysis

Most routine assays for SU utilize the Trinder reaction with uricase. The Trinder reaction detects hydrogen peroxide (H_2O_2) evolved in a solution, by producing a colored compound, which can then be determined spectrophotometrically. In the case of SU measurement, uricase is added, resulting in the production of H_2O_2, which is then measured (6).

This assay is generally reliable with between-laboratory and between-method coefficients of variation of $<5\%$. Quality assurance programs are required to ensure laboratory precision is maintained and between-laboratory differences are minimized. A recent College of American Pathologists Chemistry Survey involved over 6000 laboratories assaying the same sample. The reference SU concentration determined the uricase and isotype dilution mass spectrometry methods. Urate assays were 1 of the 4 assays to exhibit the best performance across different laboratories (7).

SU measured using the Trinder assay has demonstrated within-group sensitivity to change and also between-