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Using serum urate as a validated surrogate end point for flares in patients with gout: protocol for a systematic review and meta-regression analysis

Melanie B Morillon,1,2 Lisa Stamp,3 William Taylor,4 Jaap Fransen,5 Nicola Dalbeth,6 Jasvinder A Singh,7 Robin Christensen,1 Marissa Lassere8

ABSTRACT

Introduction: Gout is the most common inflammatory arthritis in men over 40 years of age. Long-term urate-lowering therapy is considered a key strategy for effective gout management. The primary outcome measure for efficacy in clinical trials of urate-lowering therapy is serum urate levels, effectively acting as a surrogate for patient-centred outcomes such as frequency of gout attacks or pain. Yet it is not clearly demonstrated that the strength of the relationship between serum urate and clinically relevant outcomes is sufficiently strong for serum urate to be considered an adequate surrogate. Our objective is to investigate the strength of the relationship between changes in serum urate in randomised controlled trials and changes in clinically relevant outcomes according to the 'Biomarker-Surrogacy Evaluation Schema version 3' (BSES3), documenting the validity of selected instruments by applying the 'OMERACT Filter 2.0'.

Methods and analysis: A systematic review described in terms of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines will identify all relevant studies. Standardised data elements will be extracted from each study by 2 independent reviewers and disagreements are resolved by discussion. The data will be analysed by meta-regression of the between-arm differences in the change in serum urate level (independent variable) from baseline to 3 months (or 6 and 12 months if 3-month values are not available) against flare rate, tophus size and number and pain at the final study visit (dependent variables).

Ethics and dissemination: This study will not require specific ethics approval since it is based on analysis of published (aggregated) data. The intended audience will include healthcare researchers, policymakers and clinicians. Results of the study will be disseminated by peer-reviewed publications.

Trial registration number: CRD42016026991.

INTRODUCTION

Clinicians making treatment decisions should refer to methodologically strong clinical trials examining the impact of therapy on clinically important outcomes (ie, outcomes that are important to patients). However, clinically important outcomes can be difficult to study, as the required trials need very large sample sizes or long-term patient follow-up. Thus researchers or drug developers look for alternatives. Substituting surrogate end points for the target event allows conduct of shorter and smaller trials, thus offering a solution to the dilemma, if the end points are convincing as surrogate end points.

There are obvious advantages to using biomarkers and surrogate end points, but concerns about clinical applicability and statistical validity to evaluate these aspects hinder their efficient application. A surrogate end point may be defined as an ‘objective’ laboratory measurement or a physical sign used as a substitute for a clinically meaningful end point that measures directly how a patient feels, functions or survives.1 This definition was recommended and further explored at a National Institute of Health (NIH) sponsored workshop in 1998 which agreed on definitions for biomarker.
surrogate end point and clinical end point. The agreed
definition of a biomarker states ‘a biological marker
(biomarker) is a characteristic that is objectively mea-
sured and evaluated as an indicator of normal biologic
processes, pathogenic processes or pharmacologic
responses to a therapeutic intervention.’

In gout, monosodium crystal formation occurs when
supersaturation levels of \(~6.8\) mg/dL (0.41 mmol/L) are
reached at \(37^\circ\)C. Reduction in serum urate (SU) to
\(<6\) mg/dL (0.36 mmol/L) is a key goal in the long-term
management of gout. As such SU measurement has
become an integral part of the management of
gout and a critical outcome measure in clinical
studies of gout therapies. The Outcome Measures in
Rheumatology Clinical Trials (OMERACT) Delphi exer-
cise identified SU as a mandatory outcome measure in
chronic gout studies with the highest median rating.\(^4\) SU
as a biomarker makes inherent sense given the strong
relationship between the risk of gout and SU. However,
is SU a surrogate end point of relevant clinical outcomes
such as gout attacks, tophus regression and radiological
damage?\(^5\)

**Background**

At OMERACT 8 (Malta, 2006) Lassere \(et\) \(al\)\(^6\) proposed a
schema for the evaluation of biomarkers as surrogate
end points. The schema was operationalised as a score
obtained from four domains: target outcome, study
design, statistical strength and penalties.\(^5\) This schema
was based on the NIH definitions of biomarker, surro-
gate end point and clinical end point published in
2001.\(^2\) The distinction between a surrogate and a bio-
marker was determined by the strength of association
between the biomarker and the clinical end point of
interest. To be called a surrogate, it was proposed that a
biomarker must meet the rank (score) of at least three
within the target outcome, study design and statistical
strength domains, and there must not be evidence from
a randomised controlled trial (RCT) that the use of the
biomarker caused patient harm.\(^5\)

At OMERACT 9 (Kananaskis, 2008) the soluble bio-
marker group revised the requirements for the specific
situation of a soluble biomarker being predictive of
structural radiographic damage in ankylosing spondy-
litis, psoriatic arthritis and rheumatoid arthritis.\(^7\) There
was an increased emphasis on the technical assay
requirements of the biomarker but the strength of asso-
ciation domain, while discussed in the text, did not
appear in the OMERACT 9 levels of evidence frame-
work. There was no consensus on all aspects of the
framework, and the criteria by which a soluble bio-
marker could be said to meet the levels of evidence
framework were not defined.

At OMERACT 10 (Kota Kinabalu, 2010) evidence was
presented that SU fulfilled the OMERACT 9 soluble bio-
marker requirements in terms of domain 4 (perform-
ance criteria) and there is limited evidence from
observational studies and one RCT that changes in SU
were associated with changes in patient-centred out-
comes for gout.\(^7\) However, the meeting did not endorse
SU as a biomarker for clinically relevant outcomes for
gout. The reasons for the lack of endorsement might be
that the strength of evidence was weak, the criteria for
endorsement are unclear and the chosen patient-
centred outcomes (particularly the number of flares)
were not universally held to be clinically meaningful.

In parallel to OMERACT, Lassere \(et\) \(al\)\(^5\) systematically
reviewed the biomarker–surrogate literature and modi-
ﬁﬁed the levels of evidence schema built on the
OMERACT 8 proposal which over time went through
three iterations (‘Biomarker-Surrogacy Evaluation
Schema version’ (BSES), BSES1 which was the
OMERACT 8 proposal,\(^8\) BSES2 which speciﬁed the stat-
estistical criteria more precisely\(^8\) and BSES3 which
replaced the penalties domain with a combined clinical and
pharmacological generalisability domain). BSES3 con-
tains four domains: study design, target outcome, statis-
tical evaluation and generalisability. It also speciﬁed
the kind of statistical association required to justify the link
between the biomarker and the clinical end point being
sufficiently strong to consider the biomarker as a surro-
gate end point.\(^9\)\(^10\)

In 2012 blood pressure was evaluated using the BSES3
and online material described its application and inter-
pretation.\(^10\) The BSES3 framework represents the cur-
rently best available approach to validating a biomarker
as a surrogate end point. We propose that this frame-
work be endorsed by OMERACT as the framework for
validation of biomarker–surrogates for rheumatology
clinical trials. It represents the logical extension of work
developed at OMERACT 8 and provides a clear pathway
by which a putative biomarker, soluble or otherwise, can
be evaluated, in contrast to the OMERACT 9 framework.
For example, Lassere \(et\) \(al\)\(^10\) have used trial-level data
and the BSES3 framework to convincingly show that dia-
stolic and systolic blood pressures are valid surrogate
de end points for stroke risk reduction. In a recent
meta-regression, the approach has also been used to
evaluate progression-free survival (PFS) in metastatic
renal cell carcinoma.\(^11\)

**Rationale**

We wish to use the example of SU as a soluble bio-
marker for the major clinical end point of acute gout
attacks, in the disease of gout. A minor clinical end
point would be tophus size change from baseline to
final visit, the change in the number of tophi, and pain.
Other patient relevant end points included in the
OMERACT core set of outcomes for clinical trials in
patients with chronic gout will also be evaluated in
exploratory analyses: health-related quality of life
(HRQOL), patient global assessment of disease activity
and physical disability (activities limitation).

The justification for choosing this biomarker and the
clinical end point of flares as the major end point is
described as follows:
First, SU is recommended as a treatment target by several guidelines for the management of gout.\textsuperscript{12-14} This strongly implies (although it is not stated explicitly) that changes in SU or achievement of a target level of SU will be strongly associated with clinically relevant outcomes.

Second, some regulatory bodies (e.g., Food and Drug Administration and European Medicines Agency) have tended to assume that beneficial drug effects on SU will likely have beneficial effects on clinical outcomes in gout. National Institute for Health and Care Excellence (NICE) recommended that febuxostat be available for people who are intolerant of allopurinol or who have contraindications to allopurinol.\textsuperscript{15} In other words, although NICE did not see persuasive evidence for improved clinical outcomes with the use of febuxostat, it was sufficient that the drug effectively lowered SU to below 6 mg/dL.

Third, we have previously shown that SU fulfills the technical performance criteria for a valid soluble biomarker proposed at OMERACT 9.\textsuperscript{5} Flare (acute attack) of gout is a key clinical manifestation of gout. It constitutes the primary or only manifestation for several years until persistent, tophaceous disease develops. In the expectation that effective management strategies aim to prevent chronic tophaceous disease from occurring it is justifiable to focus on attacks as the clinically relevant end point for the majority of people for gout. Although gout attacks can vary in severity (often modified by acute gout treatment), it is clear that every attack is associated with some level of symptoms and disability. Gout attacks therefore align with how a patient ‘feels or functions’ and can be reasonably be identified as a clinically relevant end point.\textsuperscript{1}

However, we recognise that other clinical outcomes are relevant and will evaluate these within the same framework. This proposal fits in the Filter 2.0 framework by making explicit and quantifying the link between Core Area domains of Pathophysiology Manifestations (biomarker) and domains of Life Impact (flare, pain, HRQOL, tophus). This framework links disease-centred variables of biological and pathological processes with patient-centred variables of how a patient feels, functions and survives as proposed at OMERACT 6.\textsuperscript{5}

Objectives

There are two objectives:

1. To determine the strength of the relationship between SU and patient-relevant outcomes, including flares, tophi, HRQOL, pain and function using meta-regression of RCTs.

2. To evaluate whether SU is a surrogate end point for clinically relevant outcomes in patients with gout as defined by the BSES3 framework.

Hypothesis

A reduction in SU will be associated with improvement in clinically relevant patient-reported outcomes including gout flares and tophus size/number.

METHODS AND ANALYSIS

Protocol and registration

The protocol for the systematic review and meta-regression analysis was prepared while planning and documenting the review methods, guarding the project team against arbitrary decision-making during review conduct and to prompt global collaboration.\textsuperscript{16} Our protocol was prepared according to the recommendations given in Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P)\textsuperscript{16} and registered on PROSPERO (CRD42016026991); this protocol and coming manuscripts will conform to the PRISMA guidelines for reporting systematic reviews and meta-analyses.\textsuperscript{17}

Eligibility criteria

The eligibility criteria for objective 1 is any RCT comparing an active drug (alone or in combination) in patients with gout with any control or placebo, with a minimum duration of 3 months. The eligibility criteria for objective 2 are any RCT, controlled clinical trial or open-label trial (OLT) comparing an (apparently) active drug (alone or in combination) in patients with gout with any control or placebo, with a minimum duration of 3 months and longitudinal observational studies of gout with a minimum duration of 3 months.

For both criteria, patients will be at least 18 years of age and meeting the preliminary American College of Rheumatology (ACR) criteria for acute arthritis of primary gout\textsuperscript{18} or given a diagnosis of gout as described by the authors.

Search and selection of trials

The following electronic databases will be searched: PubMed, EMBASE, the Cochrane Library including the Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Database of Systematic Reviews (CDSR). The search will be limited to English language studies in humans, but not limited by year of publication. The reference lists from comprehensive reviews and identified clinical trials are also manually searched.

Results of the various searches will be reviewed independently by two authors (LS and MBM). Titles and abstracts will be reviewed and if further information is required (to assess eligibility criteria), the full text will be obtained. A record of reasons for excluding studies will be kept enabling generation of a figure illustrating the flow of information through the different phases of the systematic review continuing to meta-regression analysis. Disagreements will be resolved by an independent third mediator (WT).

Data extraction

EndNote X7 software will be used to manage the records retrieved from searches of electronic databases. Results from hand searches will be tracked on a Microsoft Excel spreadsheet. A customised data
The primary purpose of this project is to evaluate the surrogacy status of SU as a ‘predictor’ of gout flare rate reduction using meta-regression of RCTs. Randomisation is essential for the causal surrogacy relationship; therefore, only RCTs will be included in the main meta-regression analysis. Non-randomised study designs will be summarised separately by meta-regression to confirm the consistency of association between the biomarker and clinical end points in other contexts. Cohort studies will be summarised as a narrative review. The analyses of both randomised and non-randomised studies contribute to the evaluation of SU within the BSESS framework.

Furthermore, in the meta-regression, the relationship between SU and clinically relevant outcomes can be undertaken using different outcome metrics. We will define these as primary and secondary analyses. In the primary analysis the dependent variable is a rate ratio (ie, an incidence density ratio) comparing the ratio of events in active versus control arms occurring at any given point in time; incidence rate is the occurrence of an event over person-time (ie, in this setting in person-months). The rate ratio allows trials of different duration to be included in the analysis. The independent variable is between arm difference of within-arm change (on-trial SU from baseline SU) of SU. Therefore, in a trial of 3 months duration, flare rate over 3 months is the dependent variable and change in SU over 3 months is the independent variable.

In secondary analyses the dependent variable is risk ratio reduction (RRR) of within trial gout flare rate. The relative ratio reduction (also called the risk ratio reduction) is the flare risk in the control arm minus the flare risk in the active arm, divided by the flare risk in the control arm (this can also be calculated by 1- relative risk [RR], where RR is the flare risk in the active arm divided by the flare risk in the control arm). Therefore the relative risk reduction (RRR) is the difference in flare risk in two arms (control-active), expressed as a percentage of the risk of the control arm.

The independent variable is within trial, by-arm difference of proportion with SU<6 mg/dL at the end of the trial.

In a RCT, by-arm difference in SU change is likely to be causal and change in SU is easily interpretable as a surrogacy metric in gout by clinicians. Relative risk
reduction is more familiar to clinicians than rate ratio but ignores trial duration. Although SU<6 mg/dL is the most common primary end point of RCTs of gout interventions, a by-arm difference in proportion achieving an SU target may be more difficult to interpret than a SU change. In addition to gout flares, the SU as a surrogate end point for two other clinical outcomes, HRQoL and tophus size, will also be evaluated as secondary clinical outcomes. If the trial does not report these outcomes, the authors will be contacted and the by-arm outcomes requested.

A quantitative evaluation of trial-level statistical surrogacy using the BSES3\textsuperscript{10} includes determining the slope coefficient of the surrogacy relationship, trial-level R\textsuperscript{2} (coefficient of determination)\textsuperscript{22} and the surrogate threshold effect (STE)\textsuperscript{23 24 25} and STE proportion (STEP)\textsuperscript{8 10} of the surrogate and true-clinical-end point relationship using data from a meta-regression of RCTs.

The STE is informative as it captures both the slope and dispersion of the surrogate-true relationship in a single metric.\textsuperscript{25} The STE is the SU difference needed to predict the primary clinical end point, gout flare rate ratio, in a new trial, if only SU is measured in the new trial. The STE is determined by comparing the difference between control and active arms SU and flare rate, respectively, as follows: (1) calculate the SU change and gout flare rate ratio based on each arm in each trial, (2) calculate the difference between control and active arms for SU change and gout flare rate ratio, (3) regress SU and gout flare rate ratio difference values using weighted by trial size errors-in-variables (specifying a reliability coefficient of 0.9) regression and by a weighted by trial-size meta-regression (as a sensitivity analysis), (4) calculate the 95% prediction limits of the regression and (5) find the SU value where the 95% prediction line intersects with the horizontal flare rate x-axis of no flare rate ratio benefit (where the flare rate ratio y-axis is equal to 1.0). Similar analyses will be explored with flare rate relative risk reduction and proportion with SU<6 mg/dL at the end of the trial. In this analysis the interest is the SU target <6 mg/dL by-arm proportion where the 95% prediction line intersects with the horizontal flare rate x-axis of no flare relative risk reduction benefit (ie, where the flare rate relative risk reduction y-axis is equal to zero). Subsequent analyses will evaluate HRQoL and tophus size as clinically relevant outcomes.

Where more than two arms from a single trial are present, the by-arm comparisons are down-weighted following A’Hern \textit{et al}\textsuperscript{26} because all within trial comparisons are not independent. In all trial comparisons, this requires that a single ‘control’ comparator is determined. In trials with a true placebo, the placebo is the control comparator. In trials without placebo, then the control comparator is an intervention arm that best reflects usual care. For example, in a five-arm trial with a true placebo there are four comparisons, and each comparison is down-weighted using analytic weights.\textsuperscript{10} This allows all arms from each trial to be evaluated in the meta-regression but adjusted for multiple comparisons with the control.

The primary and the secondary analyses are prespecified as an all drug classes combined analysis. In addition to the STE, slope, R\textsuperscript{2}_{\text{trial-level}}, and regression diagnostics, we will also evaluate the impact of effect modifiers; male sex, disease duration (<2 years, 2–10 years, more than 10 years), presence of clinical tophi (yes, no) on the SU and gout flare rate relationship. Furthermore, study design and other trial-related methodological issues, including the effect of differential cross-over, differential drop-out, whether trials included mandatory flare-prevention strategies such as mandatory colchicine and non-steroidal anti-inflammatory drug (NSAID), GRADE ratings\textsuperscript{20} and risk of bias tool\textsuperscript{10} ratings will also be explored.

The Scottish Intercollegiate Guidelines Network (SIGN) checklist\textsuperscript{27} will be used to evaluate the methodology of longitudinal observational studies of gout.

Once these statistical results are available (1) SU reduction and (2) SU target <6 mg/dL will be evaluated as a surrogate end point gout using the BSES3 criteria.

\section*{DISCUSSION}
It is important to emphasise that the evaluation of SU as a surrogate end point is for the context of using SU as an end point in clinical trials (surrogate biomarker). This is quite different to using SU to help guide clinical decision-making, for example treating to a specific SU target, or to identify that the treatment is working (monitoring biomarker). Although the meta-regression approach undertaken by the proposed study will help inform clinical decision-making, the evidence needed for treatment targets requires a different research design.

Complete application of the BSES3 framework ideally also uses individual patient level data from multiple clinical trials. Although this analysis is planned, it is contingent on agreement of relevant pharmaceutical companies to share their data and is therefore not a formal part of this protocol.

Observational studies will be included in the search strategy, but will be reported separately as a narrative review in light of the inherent risk of bias in non-randomised and uncontrolled observational study designs.

\section*{AUTHOR AFFILIATIONS}
1Musculoskeletal Statistics Unit, Department of Rheumatology, The Parker Institute, Copenhagen University Hospitals, Bispebjerg and Frederiksberg, Frederiksberg, Denmark
2Department of Rheumatology, Odense University Hospital, Svendborg, Denmark
3Department of Medicine, University of Otago, Christchurch, New Zealand
4Department of Medicine, University of Otago, Wellington, New Zealand
5JF Department of Rheumatology, Radboud University Medical Centre, Nijmegen, The Netherlands
6Department of Medicine, University of Auckland, Auckland, New Zealand
7Department of Medicine, University of Alabama at Birmingham & Birmingham Veterans Affairs Medical Center, Birmingham, Alabama, USA

\textsuperscript{5}JF Department of Rheumatology, Radboud University Medical Centre, Nijmegen, The Netherlands

\textsuperscript{6}Department of Medicine, University of Auckland, Auckland, New Zealand

\textsuperscript{7}Department of Medicine, University of Alabama at Birmingham & Birmingham Veterans Affairs Medical Center, Birmingham, Alabama, USA

\textsuperscript{1}Musculoskeletal Statistics Unit, Department of Rheumatology, The Parker Institute, Copenhagen University Hospitals, Bispebjerg and Frederiksberg, Frederiksberg, Denmark

\textsuperscript{2}Department of Rheumatology, Odense University Hospital, Svendborg, Denmark

\textsuperscript{3}Department of Medicine, University of Otago, Christchurch, New Zealand

\textsuperscript{4}Department of Medicine, University of Otago, Wellington, New Zealand

\textsuperscript{10}This allows all arms from each trial to be evaluated in the meta-regression but adjusted for multiple comparisons with the control.

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Contributors LS, WT, ND, JF, JAS and ML participated in the conception and design of this protocol. RC, JF and ML provided statistical advice for the design and analysis. LS, WT, ND, JF, RC, MBM, JAS and ML critically reviewed the manuscript for important intellectual content and approved the final version.

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