Variability in the Reporting of Serum Urate and Flares in Gout Clinical Trials: Need for Minimum Reporting Requirements

Lisa K. Stamp, Melanie B. Morillon, William J. Taylor, Nicola Dalbeth, Jasvinder A. Singh, Marissa Lassere, and Robin Christensen

ABSTRACT. ***Objective.*** To describe the ways in which serum urate (SU) and gout flares are reported in clinical trials, and to propose minimum reporting requirements.

Methods. This analysis was done as part of a systematic review aiming to validate SU as a biomarker for gout. The ways in which SU and flares were reported were extracted from each study by 2 reviewers.

Results. A total of 22 studies (10 randomized controlled trials, 3 open-label extension studies, and 9 observational studies) were identified. There were 3 broad categories of SU reporting: percentage at target SU, mean SU, and change in SU. A median of 2 (range 1–3) categories were reported across all studies. The most common method of reporting SU was percentage at target in 17/22 (77.3%) studies, with all studies reporting a target of SU < 6 mg/dl. There were 12/22 (54.5%) studies reporting mean SU at some time after study entry, with 7 (58.3%) of these reporting at more than just the final study visit. Two ways of reporting gout flares were identified: mean flare rate and percentage of participants with flares. There was variability in time periods over which flares rates were reported.

Conclusion. There is inconsistent reporting of SU and flares in gout studies. Reporting the percentage of participants who achieve a target SU reflects international treatment guidelines. SU should also be reported as a continuous variable with a relevant central and dispersion estimate. Gout flares should be reported as both percentage of participants and mean flare rates at each timepoint. (First Release December 15 2017; J Rheumatol 2018;45:419–24; doi:10.3899/jrheum.170911)

Key Indexing Terms:
GOUT SERUM URATE OUTCOME MEASURES GOUT FLARES

From the Department of Medicine, University of Otago, Christchurch, Wellington; Department of Medicine, University of Auckland, Auckland, New Zealand; Musculoskeletal Statistics Unit, The Parker Institute, Bispebjerg and Frederiksberg Hospital, Copenhagen; Department of Rheumatology, Odense University Hospital, Odense; Department of Medicine, Vejle Hospital, Vejle, Denmark; Department of Medicine, University of Alabama at Birmingham and Birmingham Veterans Affairs Medical Center, Birmingham, Alabama, USA; Department of Rheumatology, St. George Hospital, University of New South Wales (NSW), Sydney, Australia.

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L.K. Stamp, MBChB, PhD, FRACP, Department of Medicine, University of Otago; M.B. Morillon, MD, Musculoskeletal Statistics Unit, The Parker Institute, Bispebjerg and Frederiksberg Hospital, Department of Rheumatology, Odense University Hospital, and Department of Medicine, Vejle Hospital; W.J. Taylor, MBChB, PhD, FRACP, Department of Medicine, University of Otago; N. Dalbeth, MBChB, MD, FRACP, Department of Medicine, University of Auckland; J.A. Singh, MD, MPH, Department of Medicine, University of Alabama at Birmingham and Birmingham Veterans Affairs Medical Center; M. Lassere, MBBS (Hons) Grad Dip Epi, PhD, FRACP, FAFPHM, Department of Rheumatology, St. George Hospital, University of NSW; R. Christensen, MSc, PhD, Musculoskeletal Statistics Unit, The Parker Institute, Bispebjerg and Frederiksberg Hospital.

Address correspondence to Prof. L.K. Stamp, Department of Medicine, University of Otago, Christchurch, P.O. Box 4345, Christchurch, New Zealand. E-mail: lisa.stamp@cdhb.health.nz

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Publishing health research is a thriving and growing enterprise. However, the quality of reporting in most healthcare journals remains inadequate[1]. Reporting guidelines and checklists help researchers to meet those standards by providing rules or principles for specific research areas[2]. Randomized controlled trials (RCT) are the reference design standard for assessing the efficacy of interventions, but how they are planned, conducted, and reported raises important concerns[3].

A variety of outcomes can be measured in trials, and researchers must decide which of these to measure; the major outcomes should be those essential for clinical decision making. However, disagreement on the choice of outcome measures has resulted in inconsistent reporting, potential for reporting bias, and reduced quality of guidelines that are derived from the results of such trials[4].

Since 1992, The Outcome Measures in Rheumatology (OMERACT) initiative has successfully worked to improve outcome measurement collection and reporting for many rheumatologic conditions, starting with rheumatoid arthritis[5] and now covering other rheumatic diseases, including gout. For clinical trials in chronic gout, the core outcome set includes serum urate (SU), gout flares, tophus regression, and health-related quality of life[6]. For these domains to be useful,

an appropriate instrument to measure the domain and standard methods of reporting is required[7]. Such an approach allows for comparison between clinical trials, as well as evidence synthesis (including metaanalysis) of data.

SU is currently the most common primary efficacy outcome measure in clinical trials of urate-lowering therapies (ULT) and has been accepted by the US Food and Drug Administration as an adequate endpoint for regulatory approval of new therapies. SU is usually measured by the Trinder reaction with uricase. This assay has excellent measurement properties. It is generally reliable with between-laboratory and between-method coefficients of variation of < 5%. SU measured using the Trinder assay has demonstrated within-group sensitivity to change, and between-group discrimination in the context of randomized clinical trials of febuxostat, where the effect size was large (1.21–4.02) and significantly more patients achieved SU < 6.0 mg/dl at 28 days with febuxostat than with placebo (56 to 94% vs 0%, $p < 0.001$)[8].

Gout flares are typically a secondary outcome measure in clinical trials of ULT. Until recently, there has been no validated definition of gout flares and in most trials, gout flares are self-reported. Thus, it has not been possible to determine between-group differences or sensitivity[8]. However, in an RCT of canakinumab versus colchicine for gout flares, differences between treatment arms could be shown with mean number of flares per patient, those experiencing ≥ 1 flare, and time to first flare[9]. A definition of gout flares has recently been validated but has not yet been routinely used in gout studies[10,11]. Interpretation of flare rates has been further impaired by the recognition that gout flares may increase in the period after commencing ULT, and most studies use prophylaxis during early phases of clinical trials to prevent this.

While it is generally assumed that gout trialists would be guided by OMERACT recommendations regarding outcome measurement, a previous assessment of compliance with these recommendations indicated only a modest effect of the OMERACT recommendations for gout trials to date[12]. Despite SU and flares being frequently reported, the actual reporting in clinical trials has received less attention. While this issue was noted by the OMERACT gout working group[8], no consensus was reached and no further progress has been made with regard to SU reporting. Importantly, a validated definition of gout flares has been published[10,11]. As part of an ongoing study to determine whether SU is a valid surrogate for clinically important outcomes in gout trials, we have undertaken a systematic review of ULT studies.

The aim of our study was to describe the ways in which SU and gout flares are reported in clinical trials, and to propose minimum reporting requirements.

MATERIALS AND METHODS

The protocol for the full study has been published previously[13]. As per the New Zealand Health and Disability Ethics Committee, ethical approval is not required for literature review. In brief, PubMed, EMBASE, and the Cochrane Library, including the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews, were searched in February 2016. The clinical trials register was searched in November 2016 for clinical trials fulfilling the eligibility criteria that may have been published since the original search. The search was limited to English-language studies in humans, but not limited by year of publication.

The eligibility criteria for assessing ways in which SU and gout flares were reported included any randomized controlled trial, controlled clinical trials, open-label extension studies (OLE), or longitudinal observational studies comparing any ULT (alone or in combination) in people with gout with any control or placebo, with a minimum duration of 3 months.

All reports for each randomized trial and OLE included were obtained for evaluation. For each study, a matrix was constructed, listing all the ways the outcome measures were reported on SU and gout flares, and the ways these were reported were extracted from each study by 2 independent reviewers (LKS and MBM).

RESULTS

The systematic review identified 2775 records after removal of duplicates. The full text of 82 records was reviewed after title and abstract screening. A total of 22 studies comprising 10 RCT, 3 OLE studies, and 9 observational studies were identified.

SU reporting. SU reporting could be broadly grouped into 3 categories: percentage at a particular target SU, mean SU, and change in SU (Table 1). A median of 2 (range 1–3) categories were reported across all 22 studies with only 4 studies reporting in all 3 SU categories[14,15]. Within each of these 3 categories, there were at least 2 different submethods of reporting SU (Table 1). The most common method of reporting SU was percentage at a particular target SU in 17/22 (77.3%) studies. Three different target urate levels were reported at < 6 mg/dl, < 5 mg/dl, and < 4 mg/dl, with all 17 studies reporting the SU < 6 mg/dl. Eleven studies reported percentage at target SU at > 1 timepoint during the study period. There were 12/22 (54.5%) studies that reported mean SU at some time after study entry, with only 7 (58.3%) of these reporting at more than just the final study visit. There were 9 studies that reported change in SU from baseline, with the majority 6/9 (66.7%) reporting percentage change in SU. In total, there were 9 different ways of reporting SU and in the 22 studies examined, the median (range) number of ways in which SU was reported was 3 (1–6).

Gout flare reporting. There were 12/22 (54.5%) of studies that reported how gout flares were defined and of these, 79.5% specifically stated that gout flares were identified by self-report rather than by standardized criteria. There were 2 broad ways in which flares were reported: percentage of participants with a flare and mean flare rates (Table 2). There were 7/22 (31.8%) that reported the percentage of participants with a flare in the prestudy period, and an additional 5 studies had recent flare as an inclusion criterion. There were 8/22 studies (36.4%) that reported the percentage of participants with flares over the entire study period, and 11/22 (50.0%) reported flares at multiple timepoints with variations between 4 weekly and 6 monthly blocks. Only 10/22 (45.5%)

Table 1. Serum urate reporting in studies of urate-lowering therapy.

First Author and Date	Study Design	Percentage at Target Urate				Mean SU				Change in SU	
		< 6 mg/dl at Final Visit	< 5 mg/dl at Final Visit	< 4 mg/dl at Final Visit	At > 1 Visit	At Baseline Visit	At Final Visit	At > 1 Visit	Over Entire Study Period	Mean Change in SU	Mean Change in SU, %
Fraser 1987[23]	RCT					✓	✓				
McCarthy 1991[24]	Longitudinal OBS								✓		
Li-Yu 2001[25]	Longitudinal OBS	✓									
Perez-Ruiz 2002[26]	Longitudinal OBS					✓	✓		✓		
Kumar 2005[27]	OBS						✓	✓			
Becker 2005 (FACT)[28]	RCT	✓	✓	✓	✓	✓					✓
Richette 2007[29]	OBS					✓	✓	✓			
Reinders 2009[30]	RCT	✓	✓			✓	✓				✓
Becker 2009 (EXCEL)[31]	OLE	✓			✓	✓					✓
Schumacher 2009 (FOCUS)[32]	OLE	✓	✓	✓	✓	✓					✓
Becker 2010 (CONFIRMS)[33]	RCT	✓				✓					
Sundy 2011 (GOUT 1 and 2)[34]	RCT	✓			✓	✓	✓	✓			
Khanna 2011[35]	OBS cohort	✓				✓	✓			✓	
Becker 2013 (OLE Gout 1 and 2)[36]	OLE	✓			✓	✓					
Rees 2013[37]	OBS	✓	✓			✓	✓				
Bailen 2014[38]	OBS	✓				✓					✓
Huang 2014[14]	RCT	✓			✓	✓	✓	✓		✓	
Xu 2015[15]	RCT	✓			✓	✓	✓	✓		✓	
Becker 2015 (LASSO)[39]	OBS	✓	✓	✓	✓	✓					
Yu 2016[40]	RCT	✓			✓						✓
Saag 2017 (CLEAR 1)[41]	RCT	✓	✓	✓	✓	✓	✓	✓			
Bardin 2017 (CLEAR 2)[42]	RCT	✓	✓	✓	✓	✓	✓	✓			

OBS: observational study; RCT: randomized controlled trials; SU: serum urate; OLE: open-label extension.

reported a baseline flare rate prior to study entry. There were 4 (18.2%) that reported mean flare rate over the entire study period, and 4 studies that reported flares rates in time blocks ranging in duration from 2 to 6 months.

DISCUSSION

Although SU and flares are important outcome measures in studies of ULT, there is considerable variability in the way in which they are reported. In our review, all studies since 2005, except 2 observational studies, have reported percentage at target SU, with the majority reporting this at > 1 timepoint. The treat-to-target SU strategy is advocated by The American College of Rheumatology[16], the European League Against Rheumatism[17], the British Society for Rheumatology (BSR)[18], and the 3E group[19]. Apart from BSR, a target SU of < 6 mg/dl is recommended for all people with gout, with the lower target of < 5 mg/dl (advocated by BSR) suggested for those with tophi. Thus, reporting the percentage of participants who achieve a target SU appears appropriate (Table 3). The particular target reported should reflect these international guidelines.

Reporting of SU using a dichotomous variable such as the percentage of participants who achieve a particular target SU has several potential disadvantages. First, it assumes that the current targets of < 6 mg/dl and < 5 mg/dl are "correct." These targets are based on sound physiological reasoning such as the point of saturation of urate (6.8 mg/dl at pH 7.0 and temperature 37°C, and > 6 mg/dl at pH 7 and temperature 35°C), above which monosodium urate (MSU) crystals form, and below which there is dissolution of MSU crystals[20]. However, there has been no specific treat-to-target SU trial in people with gout, and there is no evidence that 1 particular target is better than another, or that the target could be raised to < 6.8 mg/dl, which is the point of saturation at physiological temperature and pH. Second, reporting SU as a dichotomous variable results in a substantial loss of information compared to reporting it as a continuous variable. Reporting as a continuous variable might allow the relationships between SU and clinically relevant outcomes to be examined in more detail. Thus, we would suggest that SU should also be reported as a continuous variable.

The timepoints at which SU should be measured should also be considered. It is recognized that the effects of urate lowering must be sustained over time for a change in clinically important outcomes in gout, such as reduction of gout flares and dissolution of tophi. Thus, it would seem appropriate that all clinical trials report the SU outcomes at multiple visits over the entire study period. There should be

Table 2. Gout flare reporting in studies of urate-lowering therapy.

First Author and Date	Flare Definition	Percentage Participants with Gout Flare			Mean Flare Rate			Flare Stated as Inclusion Criteria
		Prestudy	Over Entire Study Period	Time Blocks	Prestudy	Over Entire Study Period	Time Blocks	
Fraser 1987[23]	Self-reported	✓	✓					✓
McCarthy 1991[24]	Self-reported				✓			
Li-Yu 2001[25]	Self-reported		✓			✓		
✓erez-Ruiz 2002[26]	NR		✓			✓		
Kumar 2005[27]	NR				✓	✓		✓
Becker 2005 (FACT)[28]	Self-reported requiring treatment	✓		Day 1–Wk 8, wks 9–52, wks 48–52				
Richette 2007[29]	NR							
Reinders 2009[30]	NR		✓					
Becker 2009 (EXCEL)[31]	Self-reported	✓		2 monthly				
Schumacher 2009 (FOCUS)[32]	NR	✓		2 monthly				
Becker 2010 (CONFIRMS)[33]	NR	✓		Monthly				
Sundy 2011 (GOUT 1 and 2)[34]	Acute joint pain and swelling requiring treatment reported by patient at time and confirmed by investigator			Mos 1–3 and 4–6		✓	Mos 1–3 and 4–6	✓
Khanna 2011[35]	Self-reported				✓			
Becker 2013 (OLE Gout 1 and 2)[36]	Acute joint pain and swelling requiring treatment reported by patient at time and confirmed by investigator		✓	2 monthly			3 monthly	
Rees 2013[37]	NR	✓		3 monthly	✓	✓		✓
Bailen 2014[38]	Self-reported			2 monthly	✓			✓
Huang 2014[14]	NR			Wks 9–28 4 weekly				
Xu 2015[15]	NR	✓						
Becker 2015 (LASSO)[39]	Gout flare requiring treatment		✓		✓			✓
Yu 2016[40]	NR		✓		✓			
Saag 2017 (CLEAR 1)[41]	Self-reported requiring treatment				✓		Mos 6–12	✓
Bardin 2017 (CLEAR 2)[42]	Self-reported requiring treatment	✓		Monthly	✓		Mos 6–12	✓

NR: not reported; OLE: open-label extension.

Table 3. Suggested minimal reporting standards for SU and gout flares in gout clinical trials.

Variables	Reporting Contents	Timepoint	Rationale
Percentage at target SU	All studies to report % participants with SU < 6 mg/dl, and studies including people with tophi to report % with SU < 5 mg/dl	At baseline visit and all subsequent study visits	In accordance with current ACR, EULAR, BSR, and 3E treatment guidelines for gout
Mean SU	All studies to report actual values of mean (SD); graphical representation alone insufficient	At baseline visit and all subsequent study visits	
Mean change in SU	Not necessarily required	-	-
Mean percent change in SU	Not necessarily required	-	-
Percentage with flares	All studies to report	At baseline visit and all subsequent study visits	Flares are an important patient-centered outcome; flares may increase after starting ULT and take months to reduce
Mean flare rate	All studies to report	At baseline visit and all subsequent study visits	Flares are an important patient-centered outcome; flares may increase after starting ULT and take months to reduce

SU: serum urate; ULT: urate-lowering therapy; ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; BSR: British Society for Rheumatology.

careful consideration to the timepoints at which gout flares are reported. Given that flares may increase after starting ULT and it can take many months for flares to stop, all study timepoints should be reported rather than the rates over the entire study period reported at the final visit.

As previously reported by Dalbeth, *et al*[21], it is not

possible, given the lack of a validated flare definition, to determine within-group and between-group discrimination for gout flares. Ultimately, a multidimensional and time-integrated definition of remission in gout is required. Work toward developing remission criteria has been undertaken, with SU, gout flares, tophus, pain, and patient global assessments identified as important components[22]. Given that both SU and flares are included in this definition, standardized reporting of these elements will be required.

There is variable reporting of SU and flares in gout studies. For each randomized group, the minimum acceptable reporting standard should include SU as both a dichotomous and continuous variable, and flares as the number of patients having had ≥ 1 flare as well as the total number of flares, at all study timepoints.

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