Published in final edited form as:

J Rheumatol. 2011 July ; 38(7): . doi:10.3899/jrheum.110272.

Tophus measurement as an outcome measure for clinical trials of chronic gout: progress and research priorities

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Abstract

Despite the recognition that tophus regression is an important outcome measure in clinical trials of chronic gout, there is no agreed method of tophus measurement. A number of methods have been used in clinical trials of chronic gout, from simple physical measurement techniques to complex advanced imaging methods. This paper summarises the methods of tophus measurement that have been used and discusses the properties of these methods. Physical measurement using Vernier calipers fulfils most aspects of the Outcomes Measures in Rheumatology (OMERACT) filter. Rigorous testing of the complex methods, particularly with respect to reliability and sensitivity to change is needed, to determine the appropriate use of these methods. Further information is also required regarding which method of physical measurement is best for use in future clinical trials. The need to develop and test a patient reported measure of tophus burden is also highlighted.

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Financial Disclosures: Dr. Dalbeth has received consultant fees from Takeda and Novartis. Dr. Singh has received speaker honoraria from Abbott; research and travel grants from Allergan, Takeda, Savient, Wyeth, and Amgen; and consultant fees from Savient, URL Pharmaceuticals, and Novartis. Dr. Simon has served on the Board of Directors for Savient Pharmaceuticals and as a consultant for Takeda. Ms. MacDonald is an employee of Takeda. Dr. Becker has received consultant fees from Takeda, Savient, BioCryst, URL Pharmaceuticals, Ardea, and Regeneron.

Introduction

The tophus is a pathognomonic feature of chronic gout. This lesion represents a chronic inflammatory response to monosodium urate (MSU) crystals deposited within the subcutaneous tissues or the joint (1). Tophi have been implicated in the pathogenesis of joint damage in chronic gout, and are strongly associated with disability in this disease (2, 3). Thus, regression of tophi is likely to be an important therapeutic outcome for patients with chronic gout. In the recent Delphi exercise regarding outcome measures for clinical trials, tophus regression was identified as one of the core domains for studies of chronic gout (4). This domain was also endorsed by plenary voting at the Outcomes Measures in Rheumatology (OMERACT) 9 meeting (5).

Despite the recognition that tophus regression is an important outcome measure in clinical trials of chronic gout, there is no agreed method of tophus measurement (6). This paper summarises the methods that have been used in chronic gout studies and discusses the properties of these methods. Discussion from OMERACT 10 breakout groups on tophus measurement is summarised and results of plenary voting are shown. Finally, the future research agenda is highlighted.

Methods of tophus measurement

Eight methods of tophus measurement have been reported to date. These methods are listed in Table 1. These methods can be separated into two groups; simple methods of physical measurement that allow assessment of subcutaneous tophi, and more complex methods requiring specialised equipment or technology. Most of the complex methods involve advanced imaging techniques and allow for assessment of both subcutaneous and intra-articular tophi. The complex imaging methods may have greater sensitivity and validity, as changes within bone and joints are also captured. A detailed guide and atlas have recently been compiled to allow standardisation of these methods for use in future clinical trials (7).

The properties of each method of tophus measurement

A systematic review has been completed to identify quantitative methods of tophus measurement and to summarise the properties of the various methods of tophus measurement in detail according to the OMERACT filter (7). The findings of this review were used as the working documents in the tophus breakout sessions at the OMERACT 10 meeting. The following is a summary of the discussion in the OMERACT 10 tophus breakout groups regarding the properties of the various methods of tophus measurement.

Counting the total number of subcutaneous tophi

This method involves counting all visible tophi at each study visit. This method has been used in clinical trials of febuxostat (8, 9). Change sensitivity and between group discrimination have been demonstrated (9, 10), but reliability data are not available. Furthermore, there are no available data regarding construct and criterion validity (such as how this measure relates to other measures of tophus size, and whether the lesions counted as tophi contain MSU crystals). The breakout groups noted that although this method is feasible and simple, sensitivity to change may be limited in the early phase of a study when tophus size has reduced but tophi have not yet disappeared.

Tape measurement of subcutaneous tophus area

This method involves identification and serial measurement of an index tophus. The length and width axes are measured using a tape measure and these values are then multiplied to provide an area measurement (11). This method has been used in clinical trials of febuxostat

(8–10). Tape measurement of subcutaneous tophus area has high reliability and is sensitive to change (9, 11). However, this method was not able to differentiate between allopurinol and febuxostat treated groups (8). Furthermore, there are no available data regarding construct and criterion validity. The breakout groups also commented that measurement error may be greater using this method, compared with other physical methods such as measurement in a single axis using Vernier calipers, as two separate measurements are recorded. This issue has not been addressed in validation studies to date.

Vernier calipers for measurement of subcutaneous tophus diameter

This method involves identification and serial measurement of an index tophus. The longest diameter of the index tophus is measured using Vernier calipers (12). The properties of this method according to the OMERACT filter are summarised in Table 2. This method was considered by the breakout groups to fulfil most aspects of the OMERACT filter, although it should be noted that this method has not been used in a randomised controlled trial in chronic gout. Voting at the OMERACT 10 plenary session confirmed the conclusions of the breakout groups; with 56/68 (83%) of respondents agreeing that tophus measurement by Vernier Caliper meets the OMERACT filter for truth, discrimination and feasibility.

Digital photographic assessment of subcutaneous size

This method involves standardised digital photography and computer assisted measurement of subcutaneous tophi by a central reader. This method has been used in the phase 3 clinical trials of pegloticase with change reported as categories of response (13). Sensitivity to change and between group discrimination have been demonstrated, but reliability data and validity data are not yet available. The breakout groups agreed that this was likely to be a highly reliable method due the storage of the images in an electronic record, which allows for central reading and cross-checking of the data. However, comparison with the simple physical methods was considered important for further validation.

Ultrasonography for measurement of tophus diameter and volume

This method involves identification and serial measurement of an index tophus, and has been assessed in a longitudinal observational study of patients on urate lowering therapy (14). Measurements using ultrasonography correlate highly with magnetic resonance imaging (MRI) measurements, and intra- and interobserver reliability is good-excellent (intraclass correlation coefficient >0.82). Change sensitivity has been demonstrated, but this method was not able to discriminate between different urate lowering therapies (14). The breakout groups considered that this method might provide a useful compromise between the simple and complex methods of tophus measurement, particularly in the context of increasing availability of ultrasonography within the rheumatology clinic. However, operator variability was considered a potential problem with this method in large multi-centre studies.

Other imaging methods of assessing tophus size

MRI, conventional computed tomography (CT) and dual energy computed tomography (DECT) are further potentially useful methods of tophus size measurement (15–17). As with ultrasonography, these methods have the capacity to measure both subcutaneous and intra-articular tophi. The breakout groups commented that these methods have the benefit of storage of raw data for central reading and cross-checking. However, these methods are expensive, time-consuming and require specialised equipment and technical expertise. None of these methods have been assessed in prospective studies to date. Several groups have raised concerns regarding the reliability of MRI for tophus size assessment (14, 15). CT measurement of tophus volume is highly reliable and this imaging modality has the

additional advantage of excellent resolution of bone erosion (2, 16). However, the use of radiation and the time required to complete the volume assessments may limit the feasibility of CT. The breakout groups noted that the reliability of DECT is yet to be reported, but that this method has high face validity and might potentially be the gold standard method by which other methods could be compared.

Further considerations regarding tophus measurement as an outcome measure

The breakout groups agreed that change in tophus size should be measured in all clinical trials of chronic gout, but that the complexity of the method used may vary depending on the research question. Reporting of raw data rather than categories of response was considered ideal in order to maintain statistical power and discriminative ability. Although tophi have been shown to be strongly associated with joint damage and disability in chronic gout, little information is currently available about the patient perceptions of tophi. Furthermore, changes other than size, such as softening or improved mobility of a joint affected by tophus may be of relevance to the patient, but are not captured by the current methods. The breakout groups concluded that a patient reported measure of tophus burden/impact should be developed. This conclusion was supported by plenary voting at the OMERACT 10 meeting; 61/70 (87%) respondents agreed that a patient reported measure of tophus burden should be a priority for the research agenda.

Research priorities

The central question for further studies of tophus measurement is whether the extra information obtained from the more complex methods of measurement merits the additional cost, time and complexity. Rigorous testing of the complex methods, particularly with respect to reliability and sensitivity to change is needed, to determine the appropriate use of these methods. Further information is also required regarding the simple methods of physical measurement. In particular, it is not clear whether these methods perform differently and which would be optimal for use in future clinical trials. Ideally a simple method is needed for use in large clinical trials that has been validated against one or more of the complex methods in a smaller but rigorous validation exercise. Finally, there is a need to develop and test a patient reported measure of tophus burden. This tool may include aspects of tophus improvement such as softening, in addition to change in size. Validation of this tool against other patient reported outcomes, such as the Gout Assessment Questionnaire (GAQ) or the SF-36, would be required. Comparison should also be made between this tool and other methods of tophus measurement (both physical measurement and imaging methods).

Acknowledgments

Grant Support: Supported by resources and use of facilities at the Birmingham VA Medical Center, Alabama, USA (Dr. Singh). Dr. Khanna is the recipient of an American College of Rheumatology REF Clinical Investigator Award (Quality of Life and Healthcare Utilization in Chronic Gout). Dr. Neogi is supported by NIAMS 5K23AR55127.

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Table 1**Quantitative methods of tophus measurement**

Method	Category	Original reference describing the method
Counting the total number of subcutaneous tophi	Simple	(8)
Tape measurement of subcutaneous tophus area	Simple	(11)
Vernier calipers for measurement of subcutaneous tophus diameter	Simple	(12)
Digital photography for measurement of subcutaneous tophus area	Complex	(13)
Ultrasonography for measurement of tophus diameter and volume	Complex	(14)
Magnetic resonance imaging for measurement of tophus volume	Complex	(15)
Conventional computed tomography for measurement of tophus volume	Complex	(16)
Dual energy computed tomography for measurement of tophus volume	Complex	(17)

Table 2

Properties of the Vernier caliper method according to the OMERACT filter.

	Findings	Data source	Reference
Feasibility	Low cost, short acquisition time, high patient acceptability.	Observational cross-sectional study	(16)
Construct validity	High correlation between computed tomography and Vernier caliper measurement ($r=0.91$, $p<0.001$).	Observational cross-sectional study	(16)
Reliability	Intra-observer intraclass correlation coefficient 1.0 (95% CI 0.99, 1.0); inter-observer intraclass correlation coefficient 0.99 (95% CI 0.97, 0.99).	Observational cross-sectional study	(16)
Change sensitivity	All index tophi completely resolved with urate lowering therapy after mean of 21 months; effect size 1.83.	Non-randomised parallel treatment study	(12)
Between group discrimination	Faster resolution in benzbromarone treatment group compared to allopurinol treatment group (velocity of regression 1.21 mm/month vs. 0.57 mm/month, $p<0.01$).	Non-randomised parallel treatment study	(12)