Arthritis Care & Research
Vol. 68, No. 5, May 2016, pp 667–672
DOI 10.1002/acr.22741

ORIGINAL ARTICLE

Development of Preliminary Remission Criteria for Gout Using Delphi and 1000Minds Consensus Exercises

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Objective. **To establish consensus for potential remission criteria to use in clinical trials of gout.**

Methods. **Experts (n = 88) in gout from multiple countries were invited to participate in a web-based questionnaire study. Three rounds of Delphi consensus exercises were conducted using SurveyMonkey, followed by a discrete-choice experiment using 1000Minds software. The exercises focused on identifying domains, definitions for each domain, and the timeframe over which remission should be defined.**

Results. **There were 49 respondents (56% response) to the initial survey, with subsequent response rates ranging from 57% to 90%. Consensus was reached for the inclusion of serum urate (98% agreement), flares (96%), tophi (92%), pain (83%), and patient global assessment of disease activity (93%) as measurement domains in remission criteria. Consensus was also reached for domain definitions, including serum urate (<0.36 mm), pain (<2 on a 10-point scale), and patient global assessment (<2 on a 10-point scale), all of which should be measured at least twice over a set time interval. Consensus was not achieved in the Delphi exercise for the timeframe for remission, with equal responses for 6 months (51%) and 1 year (49%). In the discrete-choice experiment, there was a preference towards 12 months as a timeframe for remission.**

Conclusion. **These consensus exercises have identified domains and provisional definitions for gout remission criteria. Based on the results of these exercises, preliminary remission criteria are proposed with domains of serum urate, acute flares, tophus, pain, and patient global assessment. These preliminary criteria now require testing in clinical data sets.**

INTRODUCTION

Gout is a chronic disease of monosodium urate crystal (MSU) deposition (1). Early disease is characterized by intermittent flares of an acute inflammatory arthritis. With uncontrolled hyperuricemia, flares become more frequent and severe, with eventual development of tophi, joint damage, and chronic gouty arthropathy. The cornerstone of effective gout management is long-term urate lowering therapy (ULT). Over time, this therapy can lead to dissolu-

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Significance & Innovations

- There are currently no agreed upon remission criteria for gout. These consensus exercises have identified domains and provisional definitions for gout remission criteria.
- Based on the results of these exercises, preliminary remission criteria are proposed, with domains of serum urate, acute flares, tophus, pain, and patient global assessment. Remission requires all of the criteria to be fulfilled.
- There remains an important lack of consensus for the timeframe over which these domains should indicate absence of disease activity in order to define remission status. These preliminary criteria now require testing in clinical data sets and will be used as part of further consensus exercises to reach formal remission criteria for gout.

tion of MSU crystals, suppression of gout flares, and regression of tophi (2–4).

With the development of new ULT and antiinflammatory agents for management of gout, the lack of validated outcome measures for clinical trials in gout became apparent (5). For more than a decade, the Outcome Measures in Rheumatology (OMERACT) group has worked on the development of valid outcome measures for use in gout clinical trials. This work has led to endorsement of domains for both acute and chronic gout studies (and endorsement of instruments for most of the individual domains) (6–10). Whether these individual domains can be usefully captured within a single outcome measure remains uncertain, however, either as a composite score or response criteria (11,12).

Remission can be defined as the absence of signs and symptoms attributable to a disease, when the symptoms and signs can return in the future, with the understanding that the momentary absence of signs and symptoms, particularly in conditions characterized by intermittent symptoms, does not equate to remission (13). With the availability of highly effective ULT, remission in gout should be possible and, indeed, a goal of therapy. Importantly, remission in gout should represent more than simply resolution of gout flare, since the natural history of gout includes periods without symptoms and would not ordinarily be considered to represent periods of remission. To date, there are no remission criteria established for gout (5). The importance of remission or inac-

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Dr. da Rocha Castelar Pinheiro has received consulting fees from AstraZeneca (less than $10,000). Dr. Harrold has received grants from AstraZeneca, Takeda, and Pfizer (less than $10,000 each). Dr. Kerr has received a grant from AstraZeneca (more than $10,000). Dr. D. Khanna has received consulting fees and/or grants from AstraZeneca and Takeda (less than $10,000 each). Dr. P. Khanna is the Principal Investigator on a study funded by AstraZeneca and on studies funded by Ardea and Crealta. Dr. Schlesinger has received grants and/or is on the advisory board for Takeda, AstraZeneca, Novartis, and Sobi (less than $10,000 each), and has received speaking fees from Novartis and Takeda (less than $10,000 each). Dr. Singh has received grants from Takeda (more than $10,000) and Savient (less than $10,000) and consulting fees from Savient, Takeda, Regeneron, Merz, Bioiberica, Crealta, and Allergan (less than $10,000 each), and is the Principal Investigator on a study funded by Horizon through a grant to DINORA (less than $10,000). Dr. Stamp has received speaking and/or consulting fees from AstraZeneca (less than $10,000). Dr. Tausche has received speaking fees and/or honoraria from Berlin Chemie Menarini, Novartis, Ardea Bioscience, AstraZeneca, and Savient (less than $10,000 each). Dr. Terkeltaub has received consulting fees from Ardea, AstraZeneca, Sobi, Takeda, Relburn, and Revive (less than $10,000 each). Dr. Uhlig has received honoraria from AstraZeneca, Novartis, and Sobi (less than $10,000 each). Dr. Dalbeth has received consulting fees, speaking fees, and/or grants from Ardea, AstraZeneca, Fonterra, Menarini, Metabolex, Pfizer, Savient, Cymabay, Takeda, and Teijin (less than $10,000 each).

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Submitted for publication May 2, 2015; accepted in revised form September 22, 2015.

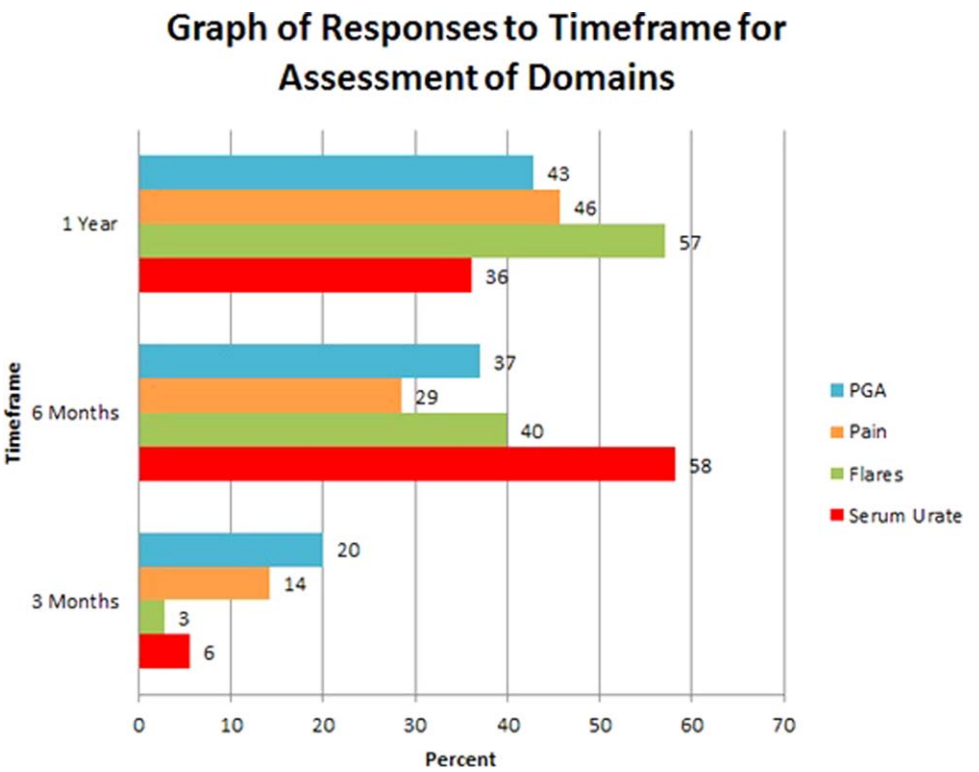

Figure 1. Preferred timeframe for remission by domain, from the third survey (percentage of respondents). PGA = patient global assessment.

tive disease as a target has become well established in other rheumatic diseases such as rheumatoid arthritis (13). The aim of this study was to establish consensus for preliminary remission criteria to use in clinical trials of gout.

METHODS

A total of 88 rheumatologists with an interest in gout from multiple countries were invited by e-mail to participate in the study. The specialists were identified from their participation in previous studies in gout. Three rounds of a Delphi consensus exercise were conducted using the commercial online service SurveyMonkey, and a discrete-choice experiment was completed using 1000Minds software (14,15). The exercises focused on identifying domains, definitions for each domain, and the timeframe over which remission should be defined. At the start of each survey, respondents were provided with the definition of remission ("the absence of signs and symptoms attributable to a disease, when the symptoms and signs can return in the future") and instructed that the proposed remission criteria were primarily intended as an outcome measure for clinical trials (13).

The Delphi exercises were conducted using SurveyMonkey. Questions focused on OMERACT-endorsed core domains for chronic gout studies, identified using qualitative methods, including patient interviews and focus groups: serum urate, tophi, number of flares, pain, and patient global assessment (6,9,10,16,17). The respondents were asked to choose whether the domain was appropriate for inclusion in remission criteria in gout and to choose a timeframe that would need to be observed to define a state of remission (1 week, 1 month, 3 months, 6 months, or 1 year). Additionally, they were asked to give a preference about how measurements for serum urate, pain, and patient global assessment would be reported, with one measurement or multiple measurements. For tophus assessment, respondents were asked whether regression in size or number or the absolute presence/absence of subcutaneous tophi would indicate remission. Consensus was defined as greater than 80% agreement in responses. For the first survey, a single choice was required, and in the subsequent surveys participants were asked to rank options. Options with less than 20% preference for first priority were discarded; all other options were included in the subsequent rounds of Delphi. Results of the previous survey were included in the questions as part of the Delphi process. Respondents were given approximately 2 weeks to respond to each survey. Surveys were repeated until consensus was reached or it became apparent that consensus could not be reached. Pain and patient global assessment questions were reworded to provide clarity to respondents based on feedback provided in the surveys and to achieve consensus.

Following the 3 rounds of Delphi exercises, a discrete-choice experiment using 1000Minds was used to further explore the relative weightings for components of remission, in particular the timeframes of 6 and 12 months. The 1000Minds software uses their mathematical algorithm PAPRIKA (Potentially All Pairwise Rankings of All Possi-

Table 1. Relative weightings of preference derived from the 1000Minds exercise

Domain, timeframe	Weighting, mean ± SD	*P**
Serum urate		
6 months	13.7 ± 7.0	2.1×10^{-7}
12 months	19.6 ± 7.5	2.1×10^{-7}
Flares		
6 months	18.7 ± 6.8	9.2×10^{-8}
12 months	29.4 ± 10.5	9.2×10^{-8}
Pain		
6 months	12.0 ± 5.7	2.4×10^{-7}
12 months	18.5 ± 6.0	2.4×10^{-7}
Patient global assessment		
6 months	11.7 ± 5.8	3.1×10^{-6}
12 months	18.6 ± 5.9	3.1×10^{-6}

* Comparison between 6 and 12 months for each domain.

ble Alternatives) to construct relative weights for each remission domain, using results of a series of pairwise comparisons of undominated pairs of all possible alternatives (a higher ranking category for 1 domain and a lower ranking category for the other domain) (15,18). Each question compares different timeframes of 2 indicators at a time and asks the respondents to choose the combination of indicators that they consider to be "more likely in remission." Sufficient pairwise comparisons are made until the algorithm identifies a series of weights that are consistent with the decisions made. The relative weightings of timeframes for each domain were assessed using a paired *t*-test. Comparisons between the responders were assessed using Student's *t*-test.

RESULTS

Delphi exercises. There were 49 respondents in the first survey (56% response rate), and 73% were men. The mean ± SD age was 51.6 ± 9.0 years, and duration in specialist rheumatology practice was 20.2 ± 10.4 years. Respondents resided in the following regions: Europe (36%), North America (29%), South America (8%), Asia (11%), and the Pacific (16%). Respondents reported seeing a mean ± SD of 34.4 ± 34.0 patients with gout per month. A total of 44 responded to the second survey (90% of initial respondents), and 37 responded to the third survey (76% of initial respondents).

Serum urate. In the first survey, 98% of respondents agreed that serum urate measurement should be included as a domain in remission criteria. Also in the first survey, respondents were asked to choose a timeframe over which serum urate would be assessed and how they would measure serum urate, whether with a single value, averaged value, or all values being <0.36 mm (6 mg/dl). There was a preference (70% of respondents) for all values being <0.36 mM (6 mg/dl). In the second survey, respondents were asked about the timeframe and measurement of serum urate combined, in order to help reach consensus. Consensus was reached that serum urate measurements should be taken at least twice over a set time period and that all measurements should be <0.36 mM (6 mg/dl) (94% agreement). The timeframe for measurement was not established after 3 Delphi rounds, with 58% choosing 6 months as their first choice, 36% choosing 1 year, and 6% choosing 3 months (Figure 1). There were no comments regarding lower serum urate levels for patients with tophaceous disease.

Tophus. In the first survey, there was consensus for tophus as a domain, with 92% choosing a form of tophus assessment. There was a spread of responses for tophus assessment, with 47% choosing absence, 42% choosing regression in size or number, and 4% choosing regression in size alone. In the second survey, there was no consensus reached on the definition of tophus response for remission, with 53% choosing absence, 43% choosing regression in size or number of tophi, and 4% reporting that tophus assessment was not useful.

Flares. In the first survey, 96% of respondents agreed that absence of acute flares should be included in remission criteria. However, after 3 Delphi rounds, consensus was not reached on the timeframe over which absence of flares should be assessed, with 1 year preferred in 57%, 6 months in 40%, and 3 months in 3% (Figure 1).

Pain. Questions that focused on the measurement of pain generated a large amount of feedback in the first survey, with the primary concern being potential difficulty distinguishing pain due to gout compared to pain due to other causes, such as osteoarthritis. Additional concerns were the possibility of recall bias and the influence of acute attacks or chronic arthropathy on pain assessment. Therefore the second survey enquired specifically about whether "pain due to gout" should be included in remission criteria. In order to reduce recall bias, the reporting of pain was also reworded to state "in timeframe of a month or longer, 2 separate measurements of pain would be averaged." A total of 60% chose to include pain in remission criteria in the second survey. During the second Delphi exercise, near consensus (77.7% choosing this option as their second or higher preference) was also reached that an average pain score of <2 on a 10-point pain scale was required for the remission definition.

The question was repeated in the third survey, with results and feedback from the second survey shown in accordance with Delphi methodology. In the final survey, consensus was reached, with 83% agreement that "pain due to gout" should be included in remission criteria, using the average of 2 separate measurements over the timeframe at equal distance apart. Consensus was not reached for the actual timeframe of assessment of pain due to gout: in the final survey, 11% preferred 1 month, 14% 3 months, 29% 6 months, and 46% 1 year (Figure 1).

Patient global assessment. In the first survey, 93% of respondents agreed that patient global assessment should be included in remission criteria. As with the pain domain, there was considerable feedback about the lack of specificity for gout and the potential for recall bias in patient global assessment. In response to these concerns, the patient global assessment measure was reworded in the second survey as a 10-cm visual analog scale or 10-point

Table 2. Proposed preliminary remission criteria for gout*

Domain	Measurement
Serum urate	<0.36 mM (6 mg/dl) at least twice over the last 12 months†
Tophus	None
Flares	None during the last 12 months
Pain	Pain due to gout <2 at least twice over the last 12 months and no values ≥2‡
Patient global assessment	Assessment of disease activity <2 at least twice over the last 12 months and no values ≥2‡

* All criteria must be achieved to meet the definition of remission.
† Measurements at equal distances apart over the 12 months, and all intervening measurements must be <0.36 mM (6 mg/dl).
‡ Measurements at equal distances apart over the 12 months, using 10-cm visual analog scale or 10-point Likert scale.

Likert scale, with the question "considering all of the ways in which your gout affects you, how well have you been doing in the last week?" (where 1 = very well and 10 = very poorly). The reporting was proposed to be 2 separate measurements over a timeframe at equal distance apart, with these measurements reported as an average. In the second survey, 84% agreed with this reporting of gout patient global assessment. During the second Delphi exercise, near consensus (77.7%) was also reached that the patient global assessment of <2 on a 10-point pain scale (i.e., ≤1 on a Likert scale and <19 mm on a 100-mm visual analog scale) was required for the remission definition. Consensus was not reached for the timeframe of the patient global assessment: in the final survey, 3 months was preferred by 20%, 6 months by 37%, and 1 year by 43% (Figure 1).

Timeframe of remission. In view of the substantial variation in timeframes for each of the domains, timeframes for overall remission were specifically explored in the final survey. There was agreement that 1 week, 1 month, and 3 months were not suitable timeframes for defining remission in gout. However, after 3 surveys, consensus was not reached regarding the timeframe, with 6 months (51%) and 1 year (49%) given approximately equal preference.

1000Minds exercise. In view of the lack of consensus from the initial Delphi exercise, a 1000Minds exercise was used to explore the timeframe over which remission should be defined. Participants who had completed all Delphi rounds were invited to participate in the 1000Minds exercise. There were 21 respondents (57% response rate). Those who responded to the 1000Minds exercise did not differ significantly from those who did not respond; responders were 62% men, with mean age 50.1 years ($P = 0.15$ compared with nonresponders), duration in specialist rheumatology was 18 years ($P = 0.09$), and reported number of patients with gout seen per month was 28.2 ($P = 0.98$). For all domains in this exercise, the 12-month period was preferred over 6 months ($P < 4 \times 10^{-6}$) (Table 1).

DISCUSSION

These consensus exercises of multinational gout experts have identified domains and provisional definitions for gout remission criteria. Based on the results of these exercises, preliminary remission criteria are proposed, with domains of serum urate, acute flares, tophus, pain, and patient global assessment (Table 2). Remission requires all of the criteria to be fulfilled.

Although this exercise has identified domains and definitions for much of the remission criteria, there is an important lack of consensus concerning the timeframe over which these domains should indicate absence of disease activity in order to define remission status. A key issue for timeframe considerations is the tradeoff between feasibility (the practicality of assessing a domain over a long period of time, e.g., 12 months) with validity (patients with active disease may not flare for periods of several months or longer). The 1000Minds exercise showed a clear preference toward 12 months. Due to the structural nature of the discrete-choice experiments as implemented in 1000Minds, 12 months would be expected to have the same or higher weighting compared to 6 months, but the finding that all domains show a highly significant preference to the longer duration has led to the provisional 12 month timeframe. This issue will be addressed further through analysis of clinical trial data, to compare measures in the first and second 6-month periods of study participation.

A limitation of the study is the relatively low response rate in the Delphi and 1000Minds exercises. The initial response rate was 56%, and 76% of those responded to the third survey. In the subsequent 1000Minds exercise, only 57% of those responding to the third survey participated, similar to comparable studies (16,17). Inclusion of nonresponder preferences may have altered the outcome of this study, but the characteristics of 1000Minds nonresponders did not differ significantly from those who completed all surveys. We also note that the proposed criteria are relatively tight and may exclude some patients with chronic gouty arthropathy from achieving remission. Patients with serum urate levels below 6 mg/dl (or 5 mg/dl if following American College of Rheumatology guidelines for patients with severe chronic tophaceous gouty arthropathy [3]) and with no flares, but with persistent tophi, would not be defined as being in remission, according to the proposed criteria. Tophi, which are composed of chronic inflammatory tissue and urate crystals, are a cardinal feature of advanced gout and are recognized as a core domain for chronic gout studies

by OMERACT (10,19). Tophi are strongly associated with disability, and there is face validity that patients with tophi are, by definition, not in remission (10,20).

Although there was strong agreement that tophus as a domain should be included in potential remission criteria, there was uncertainty in how to assess this domain, with an even split of preferences for regression of tophus versus absence. In order to finalize provisional criteria, the strictest form of assessment (absence of tophus) was chosen. Absence of tophus was preferred to tophus regression, as regression relates to a concept of change rather than the state of remission itself. If absence was deemed to be too stringent, then the alternative would be a minimal tophus burden, which would require formal definition. These definitions will be further tested in clinical trial data sets and used as part of further consensus exercises to reach formal remission criteria for gout.

There was significant feedback on patients misattributing pain from other causes in scoring pain due to gout. Although there may be issues with feasibility with this domain being in the proposed criteria, pain is a validated and OMERACT-endorsed patient-reported outcome and therefore should be included in potential remission criteria (9).

These consensus exercises have identified domains and preliminary definitions for gout remission criteria, with a provisional timeframe for assessment of 12 months. These preliminary criteria now require testing for refinement and/or validation in clinical data sets.

ACKNOWLEDGMENTS

The authors thank the additional respondents who contributed to some of the surveys: Lan Chen, Michael Doherty, N. Lawrence Edwards, Claudia Goldstein-Schainberg, Peter Gow, Tim Jansen, Vibeke Strand, and Bagus Suryana.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. de Lautour had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. De Lautour, Taylor, Dalbeth.

Acquisition of data. De Lautour, Taylor, Adebajo, Alten, Burgos-Vargas, Chapman, Cimmino, da Rocha Castelar Pinheiro, Day, Harrold, Helliwell, Janssen, Kerr, Kavanaugh, D. Khanna, P. Khanna, Lin, Louthrenoo, McCarthy, Vazquez-Mellado, Mikuls, Neogi, Ogdie, Perez-Ruiz, Schlesinger, Schumacher, Scirè, Singh, Sivera, Slot, Stamp, Tausche, Terkeltaub, Uhlig, van de Laar, White, Hisashi, Zeng, Dalbeth.

Analysis and interpretation of data. De Lautour, Taylor, Dalbeth.

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