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

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ABSTRACT

Objectives: The aim of this study was to establish consensus for potential remission criteria for 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®. 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 (93%) of disease activity as measurement domains in remission criteria. Consensus was also reached for domain definitions including serum urate (< 0.36mM), 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 six months (51%) and one 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 datasets.

SIGNIFICANCE AND 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 datasets and will be used as part of further consensus exercises to reach formal remission criteria for gout.

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 hyperuricaemia, 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 dissolution of MSU crystals, suppression of gout flares and regression of tophi (2-4).

With the development of new ULT and anti-inflammatory 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 Outcomes in Rheumatology Clinical Trials (OMERACT) group have 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). However, it remains uncertain whether these individual domains can be usefully captured within a single outcome measure, 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 inactive 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 for use in clinical trials of gout.

METHODS

Eighty eight rheumatologists with an interest in gout from multiple countries were invited by email to participate in the study. The specialists were identified from previous studies in gout. Three rounds of a Delphi consensus exercise were conducted using SurveyMonkey® and a discrete choice experiment was completed using 1000Minds® (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 a commercial online service (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 which would need to be observed to define a state of remission (one week, one month, three months, six months or one year). Additionally they

were asked to give a preference about how measurements for serum urate, pain and patient global assessment would be reported; 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 two weeks to respond to each survey. Surveys were repeated until consensus was reached or it became apparent that consensus would not be able to be reached. Pain and patient global assessment questions were re-worded to provide clarity to respondents based on feedback provided in the surveys and to achieve consensus.

Following the three 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 six and 12 months. 1000Minds® software uses a mathematical algorithm PAPRIKA (Potentially All Pairwise RanKings of all possible Alternatives) to construct relative weights for each remission domain from results of a series of pairwise comparisons of undominated pairs of all possible alternatives (a higher ranking category for one domain and a lower ranking category for the other domain) (15,18). Each question compares different timeframes of two indicators at a time and asks the respondent to choose the combination of indicators which he/she thought 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 t-tests.

RESULTS

Delphi Exercises

There were 49 respondents in the first survey (56% response rate) and 73% were male. The mean age was 51.6 (SD 9.0) years, and duration in specialist rheumatology practice was 20.2 (SD 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 of 34.4 (SD 34.0) patients with gout per month. Forty four 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. In the first survey, respondents were also asked to choose a timeframe over which serum urate would be assessed and how they would measure serum urate with: single value, averaged value or all values being below 0.36mM (6mg/dL). There was a preference (70% of respondents) for all values being below 0.36mM (6mg/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 measured at least twice over a set time period and that all measurements should be below 0.36mM (6mg/dL) (94% agreement). The timeframe for measurement was not established after three Delphi rounds, with 58% choosing six months as

their first choice, 36% choosing one year and 6% choosing three 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 three Delphi rounds consensus was not reached on the timeframe over which absence of flares should be assessed, with one year preferred in 57%, six months in 40% and three months in 3% (Figure 1).

Pain

Questions 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 re-worded to state "in timeframe of a month or longer, two separate

measurements of pain would be averaged". Sixty percent 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 two 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 one month, 14% three months, 29% six months and 46% one 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 re-worded in the second survey as a 10cm visual analogue scale or 10-point 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" (Very Well 1– Very Poorly 10). The reporting was proposed to be two separate measurements over a time-frame 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 or less on Likert scale and <19mm on a 100mm VAS) was required for the remission definition. Consensus was not reached for the timeframe of assessment of PGA: in the final survey, three months was preferred by 20%, six months by 37% and one 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 was specifically explored in the final survey. There was agreement that one week, one month and three months were not suitable timeframes for defining remission in gout. However, after three surveys consensus was not reached regarding the timeframe, with six months (51%) and one 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 did not respond to the 1000Minds® exercise; responders to the 1000Minds® exercise were 62% male, with mean age 50.1 years (P=0.15 compared with non-responders), duration in specialist rheumatology was 18 years (P=0.09) and reported number of patients with gout seen a month 28.2 (P=0.98). For all domains in this exercise, the 12 month period was preferred over six months ($P<4x10^{-6}$) (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 trade-off between feasibility (being practically able to assess a domain over a long period of time e.g. 12 months) with validity (that patients with active disease may not flare for periods of several months or longer). The 1000Minds® exercise showed a clear preference towards 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 six 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 six 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 that of comparable studies (16, 19). It is possible that inclusion of non-responders preferences may have altered the outcome of this study, but the characteristics of 1000Minds® non-responders 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. It is recognized that patients with serum urate levels below 6mg/dL (or 5mg/dL if following ACR guidelines for patients with severe chronic tophaceous gouty arthropathy) 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, 20). Tophi are strongly associated with disability and there is face validity that patients with tophi are, by definition, not in remission (10, 21).

Although there was strong agreement that tophus as a domain should be included in potential remission criteria there was uncertainly in how to assess this, 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 datasets 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 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 datasets.

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Table 1. Mean (SD) relative weightings of preference derived from the 1000Minds exercise, comparing 6 and 12 month time frames. P values refer to comparison between 6 and 12 months for each domain.

Domain	Timeframe	Mean (SD) weighting	P
Serum urate	6 months	13.7 (7.0)	$2.1x10^{-7}$
	12 months	19.6 (7.5)	
Flares	6 Months	18.7 (6.8)	$9.2x10^{-8}$
	12 Months	29.4 (10.5)	
Pain	6 months	12.0 (5.7)	$2.4x10^{-7}$
	12 months	18.5 (6.0)	
Patient global assessment	6 months	11.7 (5.8)	$3.1x10^{-6}$
	12 months	18.6 (5.9)	

Table 2. Proposed preliminary remission criteria for gout. All of the criteria must be achieved to meet the definition of remission.

Domain	Measurement
Serum urate	Serum urate < 0.36mM (6 mg/dl) at least twice over last 12 months[#], and no values ≥ 0.36mM (6 mg/dl)^
Tophus	None present
Flares	No flares during last 12 months
Pain	Pain due to gout < 2 at least twice over last 12 months[#], and no values ≥ 2*
Patient global assessment	Patient global assessment of gout disease activity < 2 at least twice over last 12 months[#], and no values ≥ 2*

*using 10cm visual analogue scale or 10-point Likert-type scale

measurements at equal distances apart over the 12 months

^ all intervening measurements must be below 0.36mM (6mg/dl)

Figure legends

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

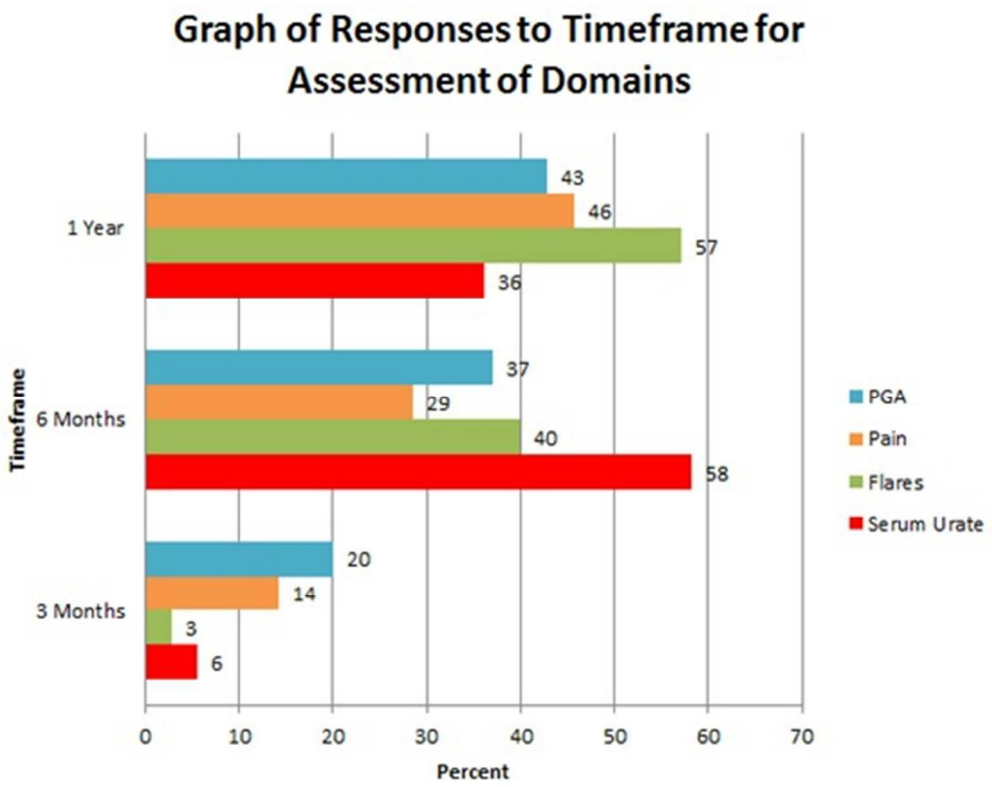

Figure 1. Preferred timeframe for remission by domain from the third survey (percentage of respondents).
PGA: patient global assessment.
146x115mm (96 x 96 DPI)