OMERACT Endorsement of Measures of Outcome for Studies of Acute Gout

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ABSTRACT. ***Objective***. To determine the extent to which participants at the Outcome Measures in Rheumatology (OMERACT) 11 meeting agree that instruments used in clinical trials to measure OMERACT core outcome domains in acute gout fulfill OMERACT filter requirements of truth, discrimination, and feasibility; and where future research efforts need to be directed.

Methods. Results of a systematic literature review and analysis of individual-level data from recent clinical studies of acute gout were presented to OMERACT participants. The information was discussed in breakout groups, and opinion was defined by subsequent voting in a plenary session. Endorsement was defined as at least 70% of participants voting in agreement with the proposition (where the denominator excluded those participants who did not vote or who voted "don't know").

Results. The following measures were endorsed for use in clinical trials of acute gout: (1) 5-point Likert scale and/or visual analog scale (0 to 100 mm) to measure pain; (2) 4-point Likert scale for joint swelling; (3) 4-point Likert scale for joint tenderness; and (4) 5-point Likert scale for patient global assessment of response to treatment. Measures for the activity limitations domain were not endorsed.

Conclusion. Measures of pain, joint swelling, joint tenderness, and patient global assessment in acute gout were endorsed at OMERACT 11. These measures should now be used in clinical trials of acute gout. (First Release Dec 15 2013; J Rheumatol 2014;41:569–73; doi:10.3899/jrheum.131246)

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Gout is the most common inflammatory arthritis, occurring more commonly than rheumatoid arthritis, with most recent prevalence estimates of 3.9% in the United States[1]. At the Outcome Measures in Rheumatology (OMERACT) 9 meeting in 2008, 5 core domains for acute gout studies were endorsed: pain, joint swelling, joint tenderness, patient global assessment, and activity limitations[2]. In addition, several discretionary domains were identified including joint impairment, work disability, joint erythema, acute phase markers, and physician global assessment. Similarly, core domains for chronic gout were also defined and endorsed.

At OMERACT 9 and OMERACT 10 in 2010, data related to measures for several domains of chronic gout were presented, and measures for pain, activity limitation, health-related quality of life, patient global, and serum urate were endorsed[3,4,5,6,7,8].

The objective of the gout workshop at OMERACT 11 in 2012 was to present data from randomized controlled trials (RCT) and observational studies related to measures of acute domains at OMERACT 10 for each domain in acute gout, and seek endorsement on specific instruments. We summarize results of OMERACT voting and reports from participant breakout sessions, and discuss a research agenda. The focus of the gout workshop was to obtain endorsement of specific instruments that measure each of the 5 core domains identified as required outcomes in acute gout trials at OMERACT 9[9].

Two companion papers reviewed the existing literature and recent acute gout studies for psychometric properties of measures for each of these domains[10,11]. This information was used to inform OMERACT participants, to assist with breakout discussion and plenary voting.

METHODS

During a 2.5-h gout workshop at OMERACT 11, we had detailed discussions related to acute gout instruments. The opening 30-min presentation consisted of a brief introduction related to acute gout, followed by a patient's description of his personal experience with gout and his life journey with the disease, followed by presentation of data analysis from RCT and observational studies related to various measures for acute gout. Subsequently, we had 4 breakout sessions, each focused on detailed discussion related to the measures of: (1) pain; (2) joint swelling and tenderness; (3) patient global assessment; and (4) activity limitations. The reporters from each of the breakout groups presented their reports at the general session. This was followed by voting by all OMERACT participants for each measure for the 5 core domains of acute gout. A majority vote of ≥ 70% in agreement with the proposition is required for OMERACT endorsement. The OMERACT executive committee had decided that the percentage vote was to be calculated from participants voting "yes" or "no" (excluding "don't know" or non-response from the denominator).

RESULTS

Breakout discussions. In relation to pain assessment, data had been presented from several trials that had applied a 5-point Likert scale, visual analog scale (VAS), and/or numeric rating scale to assess pain. Participants in the breakout group commented that the Likert pain scale has the advantages of convenience (particularly with electronic reporting diaries) compared to the VAS pain scale; VAS allows for more granular measurement, and trialists may choose either or both, because both appear to function very well in acute gout trials. Comments were also made for the future research agenda to consider the slope of pain improvement (that is, the rate of change in pain), the minimally acceptable state, time to pain resolution and achieving acceptable state, pain at rest versus pain on motion, measurement of pain behavior and pain impact, and to measure both change in pain as well as the achieved final state.

Comments were made specifically to acknowledge that pain and other patient-reported outcomes as well as measures of inflammation (joint swelling and tenderness) change so rapidly with effective treatment options for acute gout that reliability has less relevance for the psychometric assessment of any acute gout measure. This can be observed in Figure 1, which shows pain scores from a reported study of untreated acute gout over 7 days[12] superimposed upon data from an interventional study of etoricoxib and indomethacin for acute gout over 8 days[13]. It can be seen that even in untreated gout, pain improves over a matter of days. Most measures validated for acute gout domains have large effect sizes and discriminated well between groups and changes within a group, implying that these measures must be capable of demonstrating change beyond measurement error (even if the measurement error has not been formally quantified).

Data from trials that used a physician-assessed 4-point Likert scale for joint swelling and tenderness were presented. Issues with regards to joint swelling and

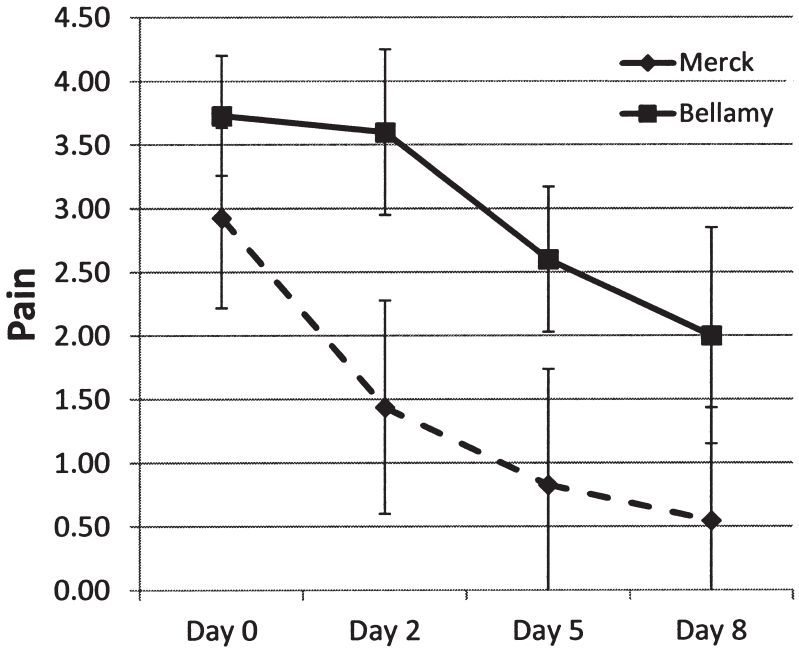

Figure 1. Pain improves quickly in acute gout (with or without treatment). The plot shows the mean (± SD) of pain scores (5-point Likert scale) from an interventional trial in acute gout (Merck, n = 339)[16] and a cohort study of untreated acute gout (Bellamy, n = 11)[12,13].

tenderness were also discussed in detail. Participants asked for clarification of whether these measures as reported were physician-assessed or patient-reported, and it was clarified that these were all physician-assessed. A suggestion was made to assess patient-reported joint swelling as another measure of this domain and perhaps this will need more validation data. Another suggestion was whether a sentinel joint should be monitored rather than multiple joints and how to assess swelling beyond a joint, when it affects the entire foot or leg.

We had presented data from acute gout trials that used a 5-point Likert scale patient global measure of change in response to treatment. The breakout groups debated the advantages and disadvantages of patient global disease measure (e.g., on a 0–10 or 0–100 scale with "no disease activity" and "severe/very severe disease activity" as anchors; or a Likert scale such as none, mild, moderate, severe, very severe) and patient global assessment of change (e.g., Likert scale), and suggested that both rather than 1 be measured in clinical trials. The groups noted that in gout trials, only Likert scales for global assessment of change were used, but similar to other rheumatic diseases, future trials need to include additional measures as discussed above. Participants also noted that patient global response to treatment scale was biased toward improvement, although they also recognized that improvement is almost the rule in the natural history of acute gout. They also suggested some other interesting versions of measures of return to pre-acute gout flare as considerations for global scales.

The current assessment of activity limitations in acute gout was generally viewed as unsatisfactory. The Health Assessment Questionnaire (HAQ) is specifically framed to assess the activity limitations over the previous week and contains many items related to upper extremity limitations. The breakout groups commented that because gout is a lower extremity predominant-arthritis with acute gout flares affecting the lower extremity, it was possible that either HAQ needed to be modified for lower extremity functional limitations, or another instrument more focused on lower extremity activity limitations should be used. Further, it was observed that acute gout evolves quickly and that an activity limitation measure should have the time frame of a day rather than a week for respondents to consider. Another issue raised was whether HAQ was a better instrument for measuring chronic as opposed to acute joint disease.

Plenary voting. The results of the voting are shown in Table 1. Overall, there was endorsement for the 5-point Likert scale and VAS (0 to 100 mm) to measure pain in acute gout; the 4-point Likert scale for joint swelling and joint tenderness; and the 5-point Likert scale for patient global assessment of response to treatment. A measure for the activity limitations domain was not endorsed.

DISCUSSION

We describe the process for OMERACT endorsement of at least 1 measure for 4 of the 5 core domains that should be included in acute gout clinical trials. Valid measures for pain (Likert scale or VAS), joint swelling, joint tenderness, and

Table 1. Voting results and endorsement of measures of acute gout for clinical trials in gout.

Domain	Measure	% Voting Yes*, %	Endorsed for Use
Pain	5-point Likert or VAS	87	Yes
Joint swelling	4-point Likert	71	Yes
Joint tenderness	4-point Likert	72	Yes
Patient global	5-point Likert	86	Yes
Activity limitation	HAQ	29	No

* From a total of 83 voting participants; the proportion is those voting yes divided by the sum of those voting yes or no; votes of "don't know" were excluded from the denominator based on an executive decision prior to the meeting related to how to count the votes. HAQ: Health Assessment Questionnaire; VAS: visual analog scale.

patient global assessment (all Likert scales) were shown to meet the OMERACT filter requirements and were endorsed by OMERACT. Development of new, high-quality outcome measures in gout is a significant advance that should allow standardization of outcome reporting in clinical trials and other clinical studies of acute gout. However, no measure for activity limitation was endorsed. HAQ, which had the most validation data, still lacked evidence for between group differences. The endorsement of all other measures provides trialists with validated outcome measures for consistent use in clinical trials of acute gout. The use of other instruments are not precluded, but it is recommended that OMERACT-endorsed instruments be concurrently assessed as a minimum. Because these are the measures of the core domains, it is recommended that at least 1 measure of each core domain be included in clinical trials or observation studies of acute gout.

Because no measure of activity limitation was endorsed, what should gout trialists do? Although we do not make a specific recommendation, we suggest that trialists consider inclusion of HAQ Disability Index, HAQ-II, or Patient-Reported Outcomes Information System/Improved HAQ[14] in clinical trials, so that enough data can be collected and analyzed to assess whether this will be a valid measure of activity limitation in patients with acute gout. Another suggestion is to include other measures of activity limitation in addition to a version of HAQ to assess which of the 2 instruments (HAQ or alternate measure) will be more sensitive to change or have better distributional properties (floor and ceiling effects). One example of an instrument that might be better for the lower limb problems experienced by most acute gout patients is the Lower Extremity Functional Scale, a 20-item self-reported scale that reflects current problems rather than problems over a specific time period[15].

Our report provides analysis of data related to measures of acute gout domains. OMERACT endorsed these measures of acute gout domains so they can now be included in clinical trials of acute gout. Future studies should assess and/or develop measures of activity limitation for acute gout clinical trials. In addition, other measures of non-core domains including work disability, joint erythema, acute phase markers, and physician global assessment should be validated using trial data, so that clear guidance regarding their use can be provided to clinical trialists.

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Part 1 Methods

Part 2 Imaging and Other Biomarkers

Part 3 Disease-specific Outcomes I

Part 4 Disease-specific Outcomes II

Part 5 The OMERACT Filter 2.0

Part 4 will appear in the April issue.