Title: Flare rate thresholds for patient assessment of gout disease activity states

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Funding sources: Funding for central study coordination and data analysis was provided by Ironwood Pharmaceuticals. Ironwood Pharmaceuticals had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for

publication. Publication of this article was not contingent upon approval by Ironwood Pharmaceuticals.

Conflict of interest: W.T. Consultant for: Pfizer, AstraZeneca, Abbvie, Roche; N. D. Grant/research support from: AstraZeneca, Amgen; Consultant for: Takeda, Pfizer, AstraZeneca, Horizon, and Kowa; K.G.S. Consultant for: Astra Zeneca, Horizon, Ironwood, SOBI, Takeda JAS has received consultant fees from Crealta/Horizon, Medisys, Fidia, UBM LLC, Trio health, Medscape, WebMD, Clinical Care options, Clearview healthcare partners, Putnam associates, Spherix, Practice Point communications, the National Institutes of Health and the American College of Rheumatology. JAS owns stock options in Amarin pharmaceuticals and Viking therapeutics. JAS is on the speaker's bureau of Simply Speaking. JAS is a member of the executive of OMERACT, an organization that develops outcome measures in rheumatology and receives arms-length funding from 12 companies. JAS serves on the FDA Arthritis Advisory Committee. JAS is a member of the Veterans Affairs Rheumatology Field Advisory Committee. JAS is the editor and the Director of the UAB Cochrane Musculoskeletal Group Satellite Center on Network Meta-analysis. JAS previously served as a member of the following committees: member, the American College of Rheumatology's (ACR) Annual Meeting Planning Committee (AMPC) and Quality of Care Committees, the

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Authorship statement: All authors had access to the data and a role in writing the manuscript.

Article type: Full Paper

Keywords: Gout, disease activity, remission

Running head: Flare thresholds in gout

Word count (main body): 3061

Abstract:

Objective: To determine the relationship between gout flare rate and self-categorization into remission, low disease activity (LDA), and patient acceptable symptom state (PASS).

Methods: Patients with gout self-categorised as remission, LDA, and PASS, and reported number of flares over the preceding 6 and 12 months. Multinomial logistic regression was used to determine the association between being in each disease state (LDA and PASS were combined) and flare count and self-reported current flare. A distribution-based approach and extended Youden index identified possible flare count thresholds for each state.

Results: Investigators from 17 countries recruited 512 participants. Remission was associated with a median recalled flare count of zero over both 6 and 12 months. Each recalled flare reduced the likelihood of self-perceived remission compared with being in higher disease activity than LDA/PASS by 52% for 6 months and 23% for 12 months, and the likelihood of self-perceived LDA/PASS by 15% and 5% for 6 and 12 months, respectively. A threshold of 0 flares in preceding 6 and 12 months was associated with correct classification of self-perceived remission in 58% and 56% of cases, respectively.

Conclusions: Flares are significantly associated with perceptions of disease activity in gout and zero flares over the prior 6 or 12 months are necessary for most people to self-categorise as being in remission. However, recalled flare counts alone do not correctly classify all patients into self-categorised disease activity states, suggesting that other factors may also contribute to self-perceived gout disease activity.

INTRODUCTION

In gout, a cardinal clinical manifestation of the disease is the gout attack or flare (1). Typically, gout flares are intensely painful but relatively short-lived and recur to a variable extent. The purpose of therapy for gout is to greatly reduce or entirely prevent these episodes, usually achieved by lowering serum urate levels. Most gout treatment guidelines recommend targeting serum urate to a level below saturation levels (2-4). Although clinical trials of urate lowering therapy will often report flares as a secondary outcome of interest, it is a key outcome of interest to patients (5) and physicians (6). It seems plausible that a patient-centred expression of gout disease activity would be characterized mainly in terms of the frequency of gout flare.

However, one of the problems with using flare frequency as an outcome measure is that it is not known how infrequent flares need to be for patients with gout to consider their disease absent (in remission), at a low level of activity not requiring therapy or at an acceptable level of activity. Without this information it is difficult to interpret outcomes expressed in flare rates.

Furthermore, when considering disease states in gout, momentary absence of signs and symptoms is not meaningful since patients may be asymptomatic between gout flares, despite active disease. Flare is considered by physicians to be an important indicator of remission and there is some suggestion that physicians prefer 6 to 12 months of flare absence as an indicator of remission (7). However, the minimum period of being flare-free that qualifies as being in remission is not well-defined. It is necessary to determine patients' opinion about this, in addition to the number of flares over the preferred time period that patients perceive as acceptable or not.

Patient-oriented disease targets in other rheumatic diseases include the concepts of 'remission', 'low disease activity' (LDA), and 'patient acceptable state' (PASS) as important disease states. 'Remission' can be defined as the absence of all signs and symptoms of the disease with the possibility of symptom recurrence (7). LDA has been defined as 'a useful target of treatment by both physician and patient, given current treatment possibilities and limitations' (8). PASS has been defined as the 'value beyond which the patient feels well' (9); that is, a low level of symptoms that the patient is happy to tolerate.

It is not yet known what frequency of gout flare would correspond to the disease activity states of remission, LDA, and PASS. Therefore, the objective of this study was to determine the experiences and opinions of patients with gout on the flare rate that corresponds to being in each of the described disease activity states.

PATIENTS AND METHODS

Patients with gout defined by the 2015 ACR/EULAR classification criteria were recruited from 17 rheumatology clinics in Asia-Pacific, North America, South America, and Europe in order to validate criteria for the presence of a gout flare (10). The study was approved by the coordinating center (University of Alabama at Birmingham – protocol number 151124003) and local institutional review boards at all study sites. All study participants accepted participation in the study through signed informed consent and were enrolled in the study regardless of current gout flare (present or absent) during the study period. Participants were asked a series of questions about how many flares they had experienced in the previous 6 and 12 months and whether or not they considered themselves to be currently experiencing a flare or not. In addition, participants

were asked to consider the highest number of flares (over 6 and 12 months) that they felt could occur and still consider themselves as being in each of the 3 disease activity states.

Participants answered questions that would classify them into none, one or more of the 3 low disease activity states, at the current time. A state of remission was defined as an affirmative response to the question "Considering the number of attacks (flares) that you have had over the last [6 or 12] months, do you think your gout has gone away?" A state of LDA was defined as a negative response to the question "Considering the number of attacks (flares) that you have had over the last [6 or 12] months, do you think you need more or stronger treatment?" A state of PASS was defined as an affirmative response to the question "Considering the number of attacks (flares) that you have had over the last [6 or 12] months, would you say that your gout control is currently satisfactory?" Similar wording has been used to anchor this disease activity state in osteoarthritis (11). Participants could self-categorise into none, any or all 3 disease activity states since each question was asked separately. Initial inspection of the flare count distributions for the LDA and PASS states showed that these appeared very similar. Furthermore, of participants not in remission who self-categorised as being in LDA or PASS, 162/225 (72%) self-categorised as being in both disease states when considering the number of flares over the prior 6 months and 154/219 (70%) for the prior 12 months. Therefore, the categories of LDA and PASS were combined for subsequent analysis. Participants were grouped into 3 mutually exclusive classes defined as: self-categorised as all of remission/LDA/PASS (remission group), self-categorised as LDA or PASS but not remission (LDA/PASS group) and self-categorised as none of the 3 disease states (high disease activity state). This grouping excluded participants who had self-categorised as being in remission but not in LDA or PASS, since such a combination was logically inconsistent.

SPSS v22 was used for analyses (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). To test the hypothesis that the different types of disease activity state were associated with different flare rates, a multinomial logistic regression model was used to model the influence of flare count and currently being in a gout flare upon membership within the disease activity class (remission, LDA/PASS, high disease activity). Separate models for considering the previous 6 months and 12 months were developed. The distribution of flare count corresponding to the highest number of flares that participants could have and still believe that they were in each of 3 disease activity states was compared using the Freidman's two-way ANOVA by ranks statistic.

Thresholds for the classification as remission, LDA/PASS and no low disease activity were identified by inspection of the distribution of flare counts, choosing 0 flares to represent remission and the 25th percentile of the flare count distribution in those classified as not being in any low disease activity state as the threshold between LDA/PASS and high disease activity. We also applied a 3-state analysis of the volume under a ROC surface (VUS) and extended Youden index implemented in R to identify the 2 thresholds between high disease activity and LDA/PASS, and between LDA/PASS and remission (12). The VUS can be interpreted as the percent correctly classified in into the corresponding 3-class structure (13). In analogy to the area under a ROC curve for 2-class structures where a value of 0.5 indicates classification by chance, for a 3-class structure a VUS value of 0.33 indicates classification by chance.

RESULTS

Between 4 January 2016 and 31 August 2016, we recruited 512 patients with gout from rheumatology clinics in 17 countries. Table 1 shows the main demographic and disease characteristics. The sample was predominately male, middle-aged and with a long disease

duration. Seventy-five percent were on urate-lowering therapies. Not all participants answered every question leading to some missing data (<2% of cases excluded from any analysis).

Supplementary Figure 1 illustrates the distribution of recalled flare counts for each disease activity state, considering 6 months (Supplementary Figure 1A) and 12 months of flares (Supplementary Figure 1B). The categories of LDA and PASS were combined for further analyses as described in the methodology. Thirteen (2.5%) participants self-categorised as remission but not LDA and PASS when considering flares over the prior 6 months and 15 (2.9%) over the prior 12 months; these participants were excluded from further analysis as providing inconsistent responses.

The recalled flare counts for each disease state group are shown in Table 2. Remission was associated with a median flare count of zero flares over both 6 and 12 months and this was different from LDA/PASS (median flare count 1 over 6 months and 3 over 12 months). Results of the multivariable analysis evaluating the independent effects of flare count and being in a current flare in relation to the self-categorised disease states are shown in Table 3. For each flare over the previous 6 and 12 months, there was a 52% (1 minus the odds ratio of being in remission 0.48) and 23% (1 minus the odds ratio of being in remission 0.77) lower likelihood of self-categorizing as remission respectively. This suggests that more recent flares had much greater influence on self-categorisation as being in remission. Each flare in the prior 6 months was associated with a 15% lower odds of self-categorizing as being in LDA/PASS, and for the prior 12 months, each flare was associated with 5% lower odds of self-categorizing as being in LDA/PASS. This suggests that more recent flares also had a stronger influence on self-categorisation as LDA/PASS. In addition we observed a very strong effect of current flare status,

with not being in a flare increasing the likelihood of a remission state by 15-fold. This effect of current flare status was similar in magnitude for the 6 month and 12 month time-horizon models.

Recalled flare count alone was not sufficiently accurate to predict self-categorised disease activity class membership. In the regression models (Table 3) the Nagelkerke pseudo-R^2 was 0.43 for 6 months of recalled flares and 0.42 for 12 months of recalled flares. Using a threshold of 0 flares for remission and the 25th percentile of the flare count distribution in those not in any low disease activity group (see Figure 1), Table 4 shows the comparison between classification based on the distribution-based thresholds of flare count (0 for remission, 1 to 2 or 3 for LDA/PASS, >2 or 3 for higher disease activity) and self-categorization. This analysis showed that these thresholds correctly predicted state membership in only 68 + 99 + 115 = 282 of 489 evaluable patients (58%) for the 6 month recalled flare question and 48 + 93 + 127 = 268 of 481 (56%) for the 12 month recalled flare question.

In an additional analysis, the VUS for 6-month flare count was 0.41 (95% CI 0.36 to 0.46) and the thresholds identified from the extended Youden index were 0 flares for the threshold between LDA/PASS and remission, and 3.5 flares for the threshold between LDA/PASS and not LDA/PASS; for 12-month flare count, the VUS was 0.38 (95% CI 0.33 to 0.43) and thresholds were 0 and 4.5.

In the final analysis, for each time-horizon, participants reported the hypothetical maximum number of flares that they would be able to experience over 6 and 12 months and still consider that they were in the associated disease-activity state. These results are shown in Table 5 and indicated that participants believed that very few flares per year were necessary to achieve any of the low disease activity states. To be in the remission or PASS state, a median of no more than zero flares over both 6 and 12 were considered necessary by participants. To be in the LDA state,

a median of no more than 1 flares over 6 and 12 months was considered necessary. There was a difference in the acceptable number of flares across the 3 disease states with all pairwise comparisons statistically significant, suggesting that there was a hierarchy of disease activity: LDA > PASS > remission in this analysis, although the difference between PASS and remission was minimal and probably not clinically relevant.

DISCUSSION

In this large, multinational study of patients with gout, recalled flare rates and especially current flare status were significantly associated with patient perception of disease activity. For each flare per year the likelihood of self-categorising as remission reduced by about one-quarter but flares within the previous 6 months influenced self-perception of current disease activity approximately twice as strongly. Consistent with a prior physician-based study to define remission criteria in gout (7), on average, zero flares were generally associated with self-categorisation as remission. When patients were asked to describe how many flares would be consistent with a hypothetical remission state over 6 and 12 months, again zero flares was the consistent answer, lending more support to the argument that this threshold is relevant for patients.

We observed similar thresholds for classification thresholds using an extended Youden index and simple inspection of the flare count distribution. However, neither approach led to correct classification in a substantial proportion of cases. The overall accuracy of flare count alone in predicting self-categorised disease activity state was less than 60% and the VUS was only around 0.4, despite trying to frame the disease status question exclusively around flares, suggesting that

other factors are relevant to patients in considering their disease status. These findings are consistent with a previous study of people with gout using a conjoint decision-making approach, which showed that patients consider other factors such as activity limitations, serum urate, and pain between attacks as other important disease outcome measures, in addition to flare frequency (5). Similarly, qualitative interviews that informed development of the Outcome Measures in Rheumatology Clinical Trials (OMERACT) domains for chronic gout studies identified a number of items in addition to flares including pain, activity limitation, tophus, and health-related quality of life (14-16). These findings also support the inclusion of flares and additional variables (tophus, pain scores, serum urate and patient global assessment) in the physician-generated provisional remission criteria (7).

The accuracy of definitions using flares recalled over the previous 6 months in distinguishing between the disease activity states of remission, LDA/PASS and no low disease activity appeared to be similar to the accuracy of definitions using flares recalled over the previous 12 months. The VUS is a 3-state equivalent to the area under a curve for a 2-state ROC analysis and these VUS values were similar for the 6-month scenario to the 12-month scenario. If further work also demonstrated that residual disease activity (as measured with additional indicators) was similar for patients categorised as remission by absence of flares over 6 months as were categorised by absence of flares over 12 months, there would seem to be no advantage in assessing remission status by the longer time-frame. This has important practical implications, particularly when designing clinical trials.

There are some limitations to the strength of conclusions that can be drawn. The flare count data were recalled retrospectively by patients and flare occurrence was not standardised so it is possible that recall-bias could influence the analysis. However, it seems plausible that recall-bias

could occur randomly in both directions, and thus dilute any effect that is present. Furthermore, a similar relationship between flare counts and disease activity status were identified when asking patients about flares using a different approach that did not rely upon recall. So it seems unlikely that recall-bias would materially affect the conclusions. In addition, we observed a likely 'availability heuristic' which is a well-described cognitive bias whereby more available information (current or more recent flare) more strongly influences perception of current disease status than less available information (more distant flares). Studies which document flares prospectively or in real time should be used in the future to confirm our findings. In particular, use of a standard flare definition or other 'gold-standard' to document flare occurrences would be of interest. It would also be of interest to ask patients about their expectation of future flare, since that could also be a factor in determining satisfaction with current gout control and treatment.

The other main limitation is that the patients were recruited from specialist clinics, whereas most people with gout are treated in primary care. It is likely that the patients in this study had more severe or treatment-resistant disease, which may limit the generalisability of the results. It is plausible that rheumatology clinic patients may have a higher flare rate threshold for thinking about disease activity status compared to primary care patients with gout. This would imply that even lower flare rates are necessary in primary care to achieve a low disease activity state and would tend to support the main conclusion that the target of care should be zero flares. On the other hand, a survey of gout patients in primary care reported a significant discrepancy between satisfaction with current treatment (79% satisfied) and frequency of recent flares (71% had flare in previous 12 months) (17). Further study in primary care patients is necessary to help understand this apparent discrepancy. This study did not collect information on serum urate

levels or give instructions to local sites about sharing serum urate information with patients. Is plausible that patients who knew that their serum urate was at goal were more likely to consider themselves in remission. Finally, we did not collect information on self-management of flares with medications such as glucocorticoids, colchicine, or non-steroidal anti-inflammatories, which could have altered the perception of disease activity during the gout flare.

This study reports the first investigation into patient perceptions of disease activity states in gout. There is no available validated patient-reported instrument in gout for self-classification into remission, LDA, and PASS with known accuracy. Thus, there is also a potential for misclassification into each disease activity state. It is possible that a different frequency distribution of disease activity status and a different relationship between recalled flare rate and disease activity would be found with different definitions. However, as far as it was possible, we phrased questions in a manner consistent with the meaning of the disease activity state in other conditions. Furthermore, it is also possible that misclassification could operate in both directions and thus be non-differential, diluting observed effects. It is therefore uncertain as to whether our main conclusions would be greatly altered.

This work has identified possible flare thresholds that are meaningful for patients with gout but the thresholds should be replicated, particularly for the states of LDA/PASS, in order to be useful for clinical assessment in practice and for clinical trial development. Other factors that could be related to the perception of remission in gout, such as tophaceous burden, quality of life, and functional scores should be investigated, with the goal of finding meaningful and comprehensive index of treatment response and remission.

In summary, flares are significantly associated with perceptions of disease activity in gout and zero flares over prior 6 or 12 months are necessary for most people to self-categorise as being in

remission. Clinical trials in the future should be designed to incorporate achievement of flare remission as an important endpoint and clinicians in practice should consider flare remission a legitimate patient-centred target of therapy. In both settings, it is necessary to determine disease activity status over a standard time-period and at a time during which the patient is not currently experiencing a flare. However, recalled flare counts alone do not accurately classify patients into self-categorised states, suggesting that other factors may also contribute to gout disease activity.

Acknowledgements:

The authors would like to thank Eve Markovitz, Michael McEwan, and Joshua Melnick for their help entering and verifying patient data at the coordinating site (UAB). Mona Thorkildsen, nurses Gina Stenberg and Ingerid Müller (Diakonhjemmet Hospital, Oslo, Norway), Dr. Michael Saddekni and nurse Stephanie Biggers (UAB) helped with participant enrolment. Drs. David Redden and Peng Li (UAB School of Public Health) gave advice on biostatistical questions. JAS contributed intellectually to the interpretation of data and analyses and participated in manuscript draft and revision, but was not involved in the conduct of study or data collection, nor received any support from the funding provided for this study. Publication of this article was not contingent upon approval by Ironwood Pharmaceuticals. Data from this paper was presented at the 2016 (Gaffo et al., Arthritis Rheumatol.2017; 68 (suppl 10)) and 2017 (Taylor et al., Arthritis Rheumatol.2017; 69 (suppl 10)) annual meetings of the American College of Rheumatology.

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Figure 1. Distribution of flare counts by disease activity state. The dotted line represents the normal distribution of the log-transformed flare count. The vertical lines represent suggested thresholds for remission (0 flares for both 6 and 12 months) and low disease activity / patient acceptable state (LDA/PASS) (1 to 2 flares for 6 months, 1 to 3 flares for 12 months). Two thresholds are required to divide the disease activity into 3 states: remission, LDA/PASS and higher disease activity.

Supplementary Figure 1. Distribution of recalled flare counts by self-categorised disease activity state **A.** Considering the previous 6 or **B.** 12 months. The dotted lines show the fitting Poisson distribution.

Table 1. Demographic and disease features (mean, SD unless otherwise specified)

Age (years)		58 (14)
Sex (% male)		455 (89%)
Ethnicity	White (%)	281 (55%)
	East Asian	51 (10%)
	Hispanic	48 (10%)
	African/Black	38 (8%)
	NZ Māori (%)	7 (1%)
	Pacific Island (%)	13 (2%)
	South Asian	7 (1%)
	Other	64 (13%)
Disease duration (years)		12 (10)
Current gout flare		157 (31%)
No. of participants self-categorised as remission	6 month	116 (23%)
	12 month	110 (22%)
No. of participants self-categorised as LDA	6 month	224 (44%)
	12 month	232 (46%)
No. of participants self-categorised as PASS	6 month	316 (62%)
	12 month	299 (59%)
Recalled number of flares (median, interquartile range)	6 months	2 (0 to 4)
	12 months	3 (1 to 8)

LDA is low disease activity; PASS is patient-acceptable symptom state

Table 2. Recalled flare count by disease activity group, considering previous 6 and 12 months of flares

	No. of flares considering previous 6 months (median, IQR)*	No. of flares considering previous 12 months (median, IQR)*
Remission	0 (0-1)	0 (0-2)
LDA/PASS	1 (0-3)	3 (1-6)
Not in any low disease activity state	4 (2-10)	6 (3-15)

*Overall test of differences between groups Kruskal-Wallis p-value<0.001. All post-hoc between group tests also significant p<0.001.

IQR is interquartile range, LDA is low disease activity, PASS is patient-acceptable symptom state

Table 3. Relation of number of recalled flares and current flare status to self-categorised disease state.

	Disease activity category*		OR (95% CI)‡
Considering the previous 6 months	Remission	No. of flares	0.48 (0.38 to 0.60)
		Current flare absent†	15.20 (5.58 to 41.37)
	LDA/PASS	No. of flares	0.85 (0.79 to 0.90)
		Current flare absent	5.74 (3.51 to 9.37)
Considering the previous 12 months	Remission	No. of flares	0.77 (0.70 to 0.85)
		Current flare absent†	15.13 (5.68 to 40.34)
	LDA/PASS	No. of flares	0.95 (0.92 to 0.97)
		Current flare absent	5.35 (3.33 to 8.60)

* The reference category is: Not in any of the 3 low disease activity states.

† The reference category is: Current flare present.

‡ The odds ratio (OR) are derived from a multinomial logistic regression model (separate models for 6 months and 12 months), where the dependent variable was disease activity category and the independent variables were flare count and presence/absence of current flare

LDA is low disease activity; PASS is patient-acceptable symptom state

Table 4. Classification of disease activity state according to distribution-based thresholds versus observed self-categorisation.

Time-horizon	Classification based on distribution-based thresholds	Remission	LDA/PASS	Not in any low disease activity state
6 months		n=103	n=223	n=163
	Flare count = 0 (n=128)	68 (53%, 66%) [a]	58	2
	Flare count = 1 to 2 (n=171)	26	99 (58%, 44%)	46
	Flare count >2 (n=190)	9	66	115 (61%, 71%)
12 months		n=94	n=215	n=172
	Flare count = 0 (n=84)	48 (57%, 51%)	34	2
	Flare count = 1 to 3 (n=164)	28	93 (56%, 43%)	43
	Flare count >3 (n=233)	18	88	127 (54%, 74%)

[a] Percentages show row and then column percentages).

LDA is low disease activity; PASS is patient-acceptable symptom state

Table 5. Hypothetical maximal flare occurrence for each disease state.

Time horizon	Disease state	Number of flares (median, interquartile range)	p-value*
Number of flares over 6 months	Remission	0 (0-0)	<0.001
	LDA	1 (0-2)	
	PASS	0 (0-1)	
Number of flares over 12 months	Remission	0 (0-0)	<0.001
	LDA	1 (0-2)	
	PASS	0 (0-2)	

*From related-samples Friedman's two-way ANOVA by ranks (all pairwise comparisons were also statistically significant)

LDA is low disease activity; PASS is patient-acceptable symptom state

FIGURE 1