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BRIEF REPORT

Relationship Between Gout Flare States and Patient-Reported Outcomes After Allopurinol Initiation

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Objective. Gout flares are the most important clinical feature of the disease. A hypothetical maximum flare occurrence in the preceding six months has been suggested to be no flares for a patient-acceptable symptom state (PASS) and only one flare for low disease activity (LDA). The aim of this analysis was to determine the relationship between gout flare states (PASS, LDA, and not in LDA or PASS [non-LDA/PASS]) and patient-reported outcomes.

Methods. Post hoc analyses of variance were undertaken using data from a 12-month randomized controlled trial involving 172 people with gout, which compared low-dose colchicine to placebo for the first 6 months while starting allopurinol with a further 6-month follow-up. Self-reported gout flares were collected monthly. Health Assessment Questionnaire (HAQ) and EuroQol 5-domain (EQ-5D-3L) were completed at 0, 3, 6 ,9, and 12 months, and the gout-specific brief illness perception questionnaire (BIPQ) was collected at months 0, 6, and 12.

Results. In the final six months of the study, 68 participants (38%) were classified as being in PASS, 34 (19%) as in LDA, and 77 (43%) as non-LDA/PASS. There was no association between gout flare states and EQ-5D-3L or HAQ. There was a statistically significant association between three of eight BIPQ items with increasing consequences, identity, and concern scores across the three states of PASS, LDA, and non-LDA/PASS.

Conclusion. The majority of people were able to achieve gout flare PASS or LDA in the second six months after commencing allopurinol. As flare burden increases, so does the impact of gout on the patient. These findings highlight the importance of flare prevention in the management of gout.

INTRODUCTION

Gout flares are the most important clinical feature for people who have gout. Gout flares affect just about every aspect of life including physical, psychological, social and family life.[1] Prevention of gout flares is therefore a key goal of management for both health care providers and people with gout. Despite this, the majority of studies of urate-lowering therapies have used serum urate (SU) as a "surrogate" measure for gout flares.[2,3] However, the burden of gout flares is multifaceted and includes the number of flares as well as the severity of each individual flare. Defining the overall flare burden for people with gout has been challenging because of variable reporting and lack of a validated flares severity definition.

Low disease activity (LDA) has been defined as "a useful target of treatment by both physician and patient, given current treatment possibilities and limitations."[4] Patient-acceptable symptom state (PASS) has been defined as the "value beyond which the patient feels well,"[5] that is, a tolerable level of symptoms for the individual. In 2021, Taylor et al[6] recruited 512 participants who answered questions about their gout flares that would classify them into one of three gout flare states: (i) remission, defined as an affirmative response to the question, "Considering

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SIGNIFICANCE & INNOVATIONS

- Flare prevention and treatment are critical aspects of gout management.
- As gout flare burden increases, so does the impact of gout on the patient.
- Most people commencing allopurinol are able to achieve gout flare patient-acceptable symptom state or low disease activity in the second six months of treatment.

the number of attacks (flares) that you have had over the last [6 or 12] months, do you think your gout has gone away?"; (ii) LDA, 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?"; or (iii) PASS, 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?" Participants also reported the hypothetical maximum number of flares that they could experience over 6 and 12 months and still consider themselves to be in the associated disease activity state. Based on these data, participants in LDA reported a median (interquartile range [IQR]) of 1 (0–2) flares and those in PASS 0 (0–1) flares in a six-month period. Similar results were observed over a 12-month period, with participants in PASS reporting a median (IQR) 0 (0–2) flares and in LDA 1 (0–2) flares.[6] Whether LDA and PASS are associated with patient-reported outcomes is unknown. The aim of this analysis was to determine the relationship between gout flare states (PASS, LDA, and not in LDA or PASS [non-LDA/PASS]) and patient-reported outcomes.

METHODS

Post hoc analyses of the 12-month "Is colchicine prophylaxis required with start-low go-slow allopurinol dose escalation in gout?" noninferiority randomized controlled trial were undertaken (ACTRN 12618001179224). Detailed methods and results of the full trial have been reported previously.[7] In brief, this was a one-year double-masked placebo-controlled noninferiority trial with participants randomized 1:1 to colchicine 0.5 mg daily or placebo for the first six months. All participants were required to have at least one gout flare in the preceding six months. All participants commenced allopurinol, increasing monthly to achieve target urate <0.36 mmol/L. The starting dose of allopurinol was 50 mg daily in those with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 and 100 mg daily in those with eGFR ≥60 mL/min/1.73 m^2. Allopurinol dose was increased monthly by 50 mg daily in those with eGFR <60 mL/min/1.73 m^2 and 100 mg daily in those with eGFR ≥60 mL/min/1.73 m^2 until serum urate was <0.36 mmol/L for three consecutive visits. Ethical approval was obtained from the Health and Disability Ethics Committee, New Zealand (18/STH/156), and all participants provided written informed consent.

Participants were seen every three months by study coordinators with intervening monthly telephone assessments. Gout flares, defined as self-reported gout flares requiring treatment were recorded at each assessment. Participants were categorized into three disease burden states at month 6 and month 12 as follows: (i) PASS, no gout flares in the preceding six months; (ii) LDA, one flare in the preceding six months; and (iii) non-LDA/PASS, more than one gout flare in the preceding six months. Participants were also classified into these three disease states based on the whole 12-month study period. The Health Assessment Questionnaire (HAQ), EuroQol-5D-3L (EQ-5D-3L) questionnaire, and the gout-specific brief illness perception questionnaire (BIPQ)[8] were collected at months 0, 6, and 12.

The baseline demographics and clinical features are summarized as means or medians with SDs or IQRs and frequencies and percentages for categorical measures. No missing data were imputed. The percentages of patients in the disease state groups were compared among randomized groups within each time interval using chi-square tests. The patient-reported outcome measures were compared among the disease state groups at each time using a one-way analysis of variance. To adjust for the multiple comparisons within each time interval, the *P* values presented are calculated using the Bonferroni adjustment.

RESULTS

Of the 200 participants enrolled, there were 183 remaining in the study at month 6 and 172 at month 12. The baseline demographics and clinical features of the 200 participants are outlined in Supplementary Table 1. Of the participants, 93% were male and had a mean ± SD age of 56 ± 15.7 years. The mean ± SD duration of gout before study entry was 11.2 ± 10.1 years, and the median (IQR) number of flares in the six months before study entry was 2 (2–4).

Disease activity states. Participants changed states between differing time periods depending on the number of flares they experienced. Over the entire 12-month study period, 32 participants (17.9%) were classified as being in PASS, 25 (14.0%) as in LDA, and 122 (68.2%) as non-LDA/PASS. In the first 6 months of the study, 61 participants (31.9%) were classified as being in PASS, 37 (19.4%) as in LDA, and 93 (48.7%) as non-LDA/PASS. In the final 6 months of the study, 68 participants (38%) were classified as being in PASS, 34 (19%) as in LDA, and 77 (43%) as non-LDA/PASS (Figure 1). There was no significant difference among randomized groups with respect to the proportion of participants fulfilling each of the 3 states in either the first or last 6 months or over the entire 12-month period.

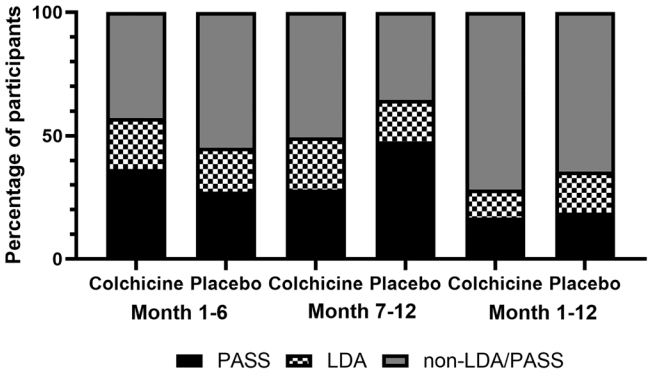

Figure 1. Percentage of participants in each disease state by randomization. LDA, low disease activity; PASS, patient-acceptable symptom state.

Association between disease activity states and patient-reported outcomes. There was no association between gout flare states and the EQ-5D-3L or HAQ (Table 1). There was a statistically significant association between three of the eight BIPQ items, namely, consequences, identity, and concern scores, with a gradient of increasing scores across the three states of PASS, LDA, and non-LDA/PASS at both months 1 to 6 and 7 to 12 (Table 1). Results were similar when PASS/LDA were combined and compared with non-LDA/PASS (Table 2).

DISCUSSION

Herein, we have shown that people with gout can achieve both gout flare LDA and PASS, but it is hard within the first year of urate-lowering therapy (ULT), and 6 months of colchicine treatment does not lead to improvements in gout flare states in the 12 months after starting ULT. Importantly, the gout flare states PASS, LDA, and non-LDA/PASS were consistently associated with three BIPQ domain scores increasing—consequences, identity, and concern—validating the impact of these gout flare states on people with gout.

Table 1. Association between PASS, LDA, and non-LDA/PASS and BIPQ items, EQ-5D-3L, and HAQ*

	PASS	LDA	Non-LDA/PASS	*P* value
Months 1–6				
Participants, n	58	35	90	
Consequences (10, severely affected)	1.4 ± 2.6	1.6 ± 2.7	3.0 ± 2.8	0.002
Timeline (10, forever)	6.2 ± 4.2	7.5 ± 3.4	7.4 ± 3.6	1.0
Personal control (10, extreme amount)	8.2 ± 2.5	8.6 ± 1.6	8.0 ± 2.2	1.0
Treatment control (10, extremely helpful)	9.0 ± 2.0	8.8 ± 2.3	8.8 ± 1.9	1.0
Identity (10, many severe symptoms)	1.7 ± 2.6	1.8 ± 1.9	3.4 ± 2.9	<0.001
Concern (10, extremely concerned)	2.1 ± 2.8	3.4 ± 2.9	4.0 ± 3.5	0.033
Understanding (10, very clearly)	7.7 ± 2.6	8.1 ± 2.1	8.2 ± 2.1	1.0
Emotional response (10, extremely affected)	1.8 ± 2.9	2.0 ± 2.5	2.7 ± 3.2	1.0
EQ-5D-3L	0.91 ± 0.17	0.95 ± 0.12	0.89 ± 0.16	0.56
HAQ	0.19 ± 0.44	0.15 ± 0.40	0.18 ± 0.41	1.0
Months 7–12				
Participants, n	66	31	75	
Consequences (10, severely affected)	1.1 ± 2.1	1.5 ± 1.9	2.7 ± 2.7	0.006
Timeline (10, forever)	7.5 ± 3.6	7.2 ± 3.6	8.3 ± 3.1	1.0
Personal control (10, extreme amount)	8.4 ± 2.5	8.7 ± 1.2	8.2 ± 2.2	1.0
Treatment control (10, extremely helpful)	8.9 ± 2.3	8.9 ± 2.0	9.2 ± 1.5	1.0
Identity (10, many severe symptoms)	0.8 ± 1.3	1.7 ± 1.9	2.8 ± 2.6	<0.001
Concern (10, extremely concerned)	1.9 ± 2.9	3.6 ± 3.4	3.8 ± 3.3	0.016
Understanding (10, very clearly)	8.4 ± 1.9	8.6 ± 1.9	8.6 ± 2.0	1.0
Emotional response (10, extremely affected)	1.4 ± 2.3	2.6 ± 2.9	1.7 ± 2.5	1.0
EQ-5D-3L	0.93 ± 0.13	0.93 ± 0.14	0.90 ± 0.16	0.98
HAQ	0.18 ± 0.38	0.12 ± 0.30	0.18 ± 0.41	1.0
Months 1–12				
Participants, n	31	23	118	
Consequences (10, severely affected)	1.1 ± 2.0	1.0 ± 1.9	2.2 ± 2.6	0.14
Timeline (10, forever)	7.6 ± 3.5	7.1 ± 3.6	8.0 ± 3.4	1.0
Personal control (10, extreme amount)	8.1 ± 2.9	8.9 ± 1.9	8.4 ± 2.1	1.0
Treatment control (10, extremely helpful)	8.3 ± 2.9	8.8 ± 2.3	9.2 ± 1.4	0.59
Identity (10, many severe symptoms)	0.5 ± 0.96	0.8 ± 1.2	2.3 ± 2.4	<0.001
Concern (10, extremely concerned)	2.1 ± 3.0	1.7 ± 2.4	3.5 ± 3.4	0.09
Understanding (10, very clearly)	8.2 ± 1.8	8.4 ± 2.2	8.6 ± 1.9	1.0
Emotional response (10, extremely affected)	1.3 ± 2.4	1.4 ± 2.4	2.0 ± 2.6	1.0
EQ-5D-3L	0.94 ± 0.13	0.97 ± 0.09	0.90 ± 0.15	0.90
HAQ	0.22 ± 0.42	0.07 ± 0.26	0.18 ± 0.39	1.0

* Data presented are mean ± SD, and *P* values are Bonferroni corrected. BIPQ, brief illness perception questionnaire; EQ-5D-3L, EuroQol 5-domain; HAQ, Health Assessment Questionnaire; LDA, low disease activity; PASS, patient-acceptable symptom state.

Table 2. Association between PASS/LDA and non-LDA/PASS and BIPQ items, EQ-5D-3L, and HAQ*

	PASS/LDA	Non-LDA/PASS	*P* value
Months 1–6			
Participants, n	93	90	
Consequences (10, severely affected)	1.5 ± 2.6	3.0 ± 2.8	0.002
Timeline (10, forever)	6.7 ± 4.0	7.4 ± 3.5	1.0
Personal control (10, extreme amount)	8.3 ± 2.2	8.0 ± 2.2	1.0
Treatment control (10, extremely helpful)	8.9 ± 2.1	8.8 ± 1.9	1.0
Identity (10, many severe symptoms)	1.7 ± 2.4	3.4 ± 2.9	<0.001
Concern (10, extremely concerned)	2.6 ± 3.0	4.0 ± 3.5	0.03
Understanding (10, very clearly)	7.9 ± 2.4	8.2 ± 2.1	1.0
Emotional response (10, extremely affected)	1.9 ± 2.7	2.7 ± 3.2	0.47
EQ-5D-3L	0.92 ± 0.15	0.89 ± 0.16	0.50
HAQ	0.17 ± 0.42	0.18 ± 0.41	1.0
Months 7–12			
Participants, n	97	75	
Consequences (10, severely affected)	1.3 ± 2.0	2.7 ± 2.7	0.001
Timeline (10, forever)	7.4 ± 3.6	8.3 ± 3.1	0.70
Personal control (10, extreme amount)	8.5 ± 2.2	8.2 ± 2.2	1.0
Treatment control (10, extremely helpful)	8.9 ± 2.2	9.2 ± 1.5	1.0
Identity (10, many severe symptoms)	1.1 ± 1.5	2.8 ± 2.6	<0.001
Concern (10, extremely concerned)	2.4 ± 3.2	3.8 ± 3.3	0.08
Understanding (10, very clearly)	8.5 ± 1.9	8.6 ± 2.0	1.0
Emotional response (10, extremely affected)	1.8 ± 2.5	1.7 ± 2.5	1.0
EQ-5D-3L	0.93 ± 0.13	0.90 ± 0.16	0.41
HAQ	0.16 ± 0.36	0.18 ± 0.41	1.0
Months 1–12			
Participants, n	54	118	
Consequences (10, severely affected)	1.1 ± 2.0	2.2 ± 2.6	0.04
Timeline (10, forever)	7.4 ± 3.5	8.0 ± 3.4	1.0
Personal control (10, extreme amount)	8.4 ± 2.5	8.4 ± 2.1	1.0
Treatment control (10, extremely helpful)	8.5 ± 2.6	9.2 ± 1.4	1.0
Identity (10, many severe symptoms)	0.7 ± 1.1	2.3 ± 2.4	<0.001
Concern (10, extremely concerned)	1.9 ± 2.8	3.5 ± 3.4	0.026
Understanding (10, very clearly)	8.3 ± 2.0	8.6 ± 1.9	1.0
Emotional response (10, extremely affected)	1.3 ± 2.4	2.0 ± 2.6	1.0
EQ-5D-3L	0.95 ± 0.12	0.90 ± 0.15	0.11
HAQ	0.16 ± 0.37	0.18 ± 0.39	1.0

* *P* values are Bonferroni corrected. BIPQ, brief illness perception questionnaire; EQ-5D-3L, EuroQol 5-domain; HAQ, Health Assessment Questionnaire; LDA, low disease activity; PASS, patient-acceptable symptom state.

Of note, the HAQ-II and EQ-5D-3L were not associated with gout flare states. Although activity limitation is recognized as an important outcome in gout studies, it has been noted that the HAQ-II has significant floor effects, which limits its ability to differentiate the spectrum of disability in people with gout.[9,10] Neither the HAQ nor EQ-5D-3L are specific for gout and may reflect the impact of comorbidities that are commonly associated with gout. Previous studies have reported an association between the number of gout flares and the gout-related Health-Related Quality of Life Gout Impact Scale, but not the HAQ-Disability Index.[11] In another study, participants with inadequately controlled gout (defined as SU >0.36 mmol/L or ≥2 flares in the previous 12 months) had worse health-related quality of life as measured by EQ-5D-3L compared with those with adequately controlled gout (defined as SU ≤0.36 mmol/L and 0 flares in the previous 12 months) (EQ-5D-3L 0.790 vs 0.877; difference –0.087; *P* <0.001).[12] However, we were unable to show a similar association with the different gout flare states.

It is important to note that the study population was 93% male. Although this reflects a typical gout trial population, women often experience higher disease severity, have more negative illness perceptions, and experience higher impact on daily activities.[13,14] Although the number of women in our study were too small to enable analysis by gender, we would expect the observed effects to be even more pronounced in women.

These data contribute to our understanding of the impact and burden of gout flares in people with gout, highlighting their concern about this core clinical manifestation of the disease. In the long term, excellent serum urate control is important. However, it is also essential that health care professionals support people with gout to prevent and manage flares as a core part of gout management.

Strengths of this study include the standardized study protocols, prospective gout flare event ascertainment, and use of outcomes of relevance to patients. Limitations include some loss to follow-up, albeit minimal; the use of subjective assessments; and

the short study design, which did not allow for assessment beyond one year. It is well recognized that gout flares can paradoxically increase after starting ULT. Given this peak in flares after starting ULT, it is not surprising that LDA and PASS are hard to achieve in the first six months of starting ULT even with anti-inflammatory prophylaxis with colchicine. Over time, there is a gradual reduction in gout flares such that, by the second year of ULT, if target serum urate is achieved, flares may cease altogether or occur less frequently.[3] Thus, it is likely that longer trials beyond 12 months are required to see the full effect of ULT on achievement of the disease activity states. Finally, we did not asked participants in the study whether they considered that their flare frequency aligned with the ascribed disease state.

The majority of people (57%) were able to achieve PASS or LDA in the second six months after commencing ULT. As the flare burden increases, so does the impact of gout on the patient. These findings highlight the importance of flare prevention in the management of gout.

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AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Stamp confirms that all authors have provided the final approval of the version to be published, and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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