

Gout flare treatment efficacy

What represents treatment efficacy in long-term studies of gout flare prevention? An interview study of people with gout

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ABSTRACT

Objective: The patient experience of gout flares is multidimensional with several contributing factors, including pain intensity, duration and frequency. There is currently no consistent method for reporting gout flare burden in long-term studies. This study aimed to determine which factors contribute to patient perceptions of treatment efficacy in long-term studies of gout flare prevention.

Methods: This study involved face-to-face interviews with people with gout using visual representations of gout flare patterns. Participants were shown different flare scenarios over a hypothetical 6-month treatment period portraying varying flare frequency, pain intensity and flare duration. The participants were asked to indicate and discuss which scenario they believed was most indicative of successful treatment over time. Quantitative data relating to the proportion of participants selecting each scenario were reported using descriptive statistics. A qualitative descriptive approach was used to code and categorize the data from the interview transcripts.

Results: Twenty-two people with gout participated in the semi-structured interviews. All three factors of pain intensity, flare duration and flare frequency influenced participants' perception of treatment efficacy. However, a shorter flare duration was the most common indicator of successful treatment, with half of participants (n = 11, 50%) selecting the scenario with a shorter flare duration over those with less painful flares.

Conclusion: Flare duration, flare frequency, and pain severity are all considered by patients with gout when considering treatment efficacy over time. Long term studies of gout should ideally capture all of these factors to better represent patients' experience of treatment success.

INTRODUCTION

Gout is a common inflammatory arthritis caused by monosodium urate crystal deposition in tissues [1] and is characterised by episodes of painful joint inflammation, known as ‘gout flares’. Gout flares are sporadic and unpredictable, with patients typically experiencing recurrent flares interspersed with pain-free inter-critical periods. The patient experience of gout flares is multi-dimensional, causing major disability and impacting many aspects of the patients’ lives, including; physical function, social and family life, physiological wellbeing and self-care [2, 3].

Measurement of gout flares is recognised by the Outcome Measures in Rheumatology (OMERACT) group as a core outcome domain for clinical research investigating the long-term treatment of gout [4]. However, there is no standardized method for measuring flare burden over time in clinical trials and there is inconsistency in the methods used to measure and report flares in long term studies of gout flare prevention [5].

Measurement of gout flares is made particularly challenging by the wide variation in flare patterns over time which differ in frequency, pain intensity, and flare duration [6]. The most common method used in clinical trials to capture flares over time is to report the proportion of patients experiencing at least one flare during the follow-up period, without any further information about flare severity [7]. The multi-dimensional patient experience of gout flares clearly goes far beyond what is routinely measured in research or clinical settings [7, 8].

There is also discordance evident between physicians and patients on the presence of a gout flare, where patient-reported flares associated with less pain, swelling and warmth are not regarded as flares by physicians [9].

There is a need to establish a standardised method for measuring gout flares that can be used in clinical research investigating the efficacy of treatments targeting flare prevention. An

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important step is to gain an understanding of which aspects of gout flares are most important to patients when considering treatment efficacy. This knowledge would better allow research, management and treatment of patients with gout to accurately address and target areas of most concern to patients experiencing flares. This study aimed to determine which factors contribute to patient perceptions of treatment efficacy in long-term studies of gout flare prevention.

METHODS

Design

This study involved semi-structured face-to-face interviews with people with gout, using visual representations of gout flare patterns. A critical realism epistemological position was used to analyse the data in order to understand which factors of gout flares are considered to be indicative of treatment efficacy over time.

Participants

Ethical approval for the study was obtained from the University of Auckland Human Participants Ethics Committee (UAHPEC 023965). Participants in this study were recruited for a qualitative interview study, which has been reported previously [2]. The sample size in the study was determined by a purposive sampling framework to ensure a broad and diverse representation of demographic variables (age, ethnicity, sex) and gout disease characteristics (disease duration, tophaceous gout, flare frequency). Recruitment occurred concurrently with analysis and continued until theoretical saturation was reached. In brief, patients with gout, according to the ACR/EULAR 2015 Gout Classification Criteria [10], were recruited from existing databases of patients with gout who have participated in research at the Clinical Research Centre, University of Auckland, New Zealand and had consented to be contacted

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for future studies. The inclusion criteria were: aged over 18 years, and English-speaking. Participants were excluded if they had a cognitive impairment or had other forms of autoimmune inflammatory arthritis. The sampling framework ensured that participants represented demographic diversity (age, gender, ethnicity) and gout disease characteristics (disease duration, flare frequency).

Data collection

In-depth, semi-structured face-to-face interviews were conducted by a rheumatologist who was not involved in the medical care of the participants (AGG). The interviews took place in a private room at the Clinical Research Centre (University of Auckland, New Zealand) and lasted between 20 and 45 minutes [2]. The portion of the interviews analysed in the current study were aimed at understanding how the following three factors of gout flares over time are considered by patients to be indicative of successful treatment: pain severity, flare duration and flare frequency. These factors were chosen based on the current reporting of flare prevention outcomes in gout studies [7].

The participants were asked to imagine they were taking part in a study testing a new treatment, which aimed to reduce gout flares over a 6-month period. Each participant was presented with three different scenarios representing three flare patterns over the treatment period: Scenario One: “A single gout flare which reaches a maximum pain of ten and lasts one week long”; Scenario Two: “A single gout flare which reaches a maximum pain of five and lasts two weeks long”; and Scenario Three: “Two gout flares, with each reaching a maximum pain of five and lasting one week long”. Participants were also shown each of the three scenarios in the form of graphs with time on the x axis and pain on the y axis, providing a visual representation of the scenarios (**Figure 1**). The three flare scenarios were developed by two rheumatologists with expertise in gout research (WTJ, ND). The scenarios were

designed based on data collected through daily flare diaries during a six-month gout trial, and reflect the variable patterns of gout flares over time [6]. For each visual representation, the area under the pain-time curve was the same. The participants were asked to indicate which scenario they believed indicated the treatment was working the best and why. An interview schedule containing key focused, open-ended questions and probes was used to encourage conversation.

Each interview was audio-recorded, transcribed ad verbatim and anonymised to ensure confidentiality. Participants had the opportunity to review the transcripts to check for completeness and representativeness. Demographic and clinical data were also obtained during the participants' study visit, including age at onset of gout, ethnicity, and presence and history of clinical features of gout and treatment.

Data analysis

Quantitative data relating to the proportion of participants selecting each scenario were reported using descriptive statistics. A qualitative descriptive approach guided study design. Thematic analysis was used to code and categorize the data from the interview transcripts under three pre-determined themes (pain severity, flare frequency and flare duration). This approach reflects the flexibility of thematic analysis which allows coding of data to fit within a pre-determined framework driven by the researcher's analytic interest in the area [11]. The themes were chosen based on the current reporting of flare prevention outcomes in gout studies [7] and reflect the intentional differences between the three flare scenarios used in the interviews. Transcripts were initially coded by a single researcher (JH) using NVivo software (QSR International Property Ltd., Version 12). Initial coding was reviewed by two

further researchers (SS, ND) and final coding was agreed upon by all authors. Illustrative quotes from transcripts were selected to provide evidence for each theme.

RESULTS

Participant characteristics

A total of 25 eligible patients with gout were invited to participate; of which 3 declined, and 22 participated in the interviews. Demographic and gout disease characteristics are shown in **Table 1**. The majority of participants were New Zealand European middle-aged males. All participants had experienced at least one gout flare in the previous 12 months.

Attributes of gout flares indicative of treatment success

Scenario One (a single gout flare which reaches a maximum pain of ten and lasts one week long) was perceived by half of participants (n = 11, 50%) as being indicative of the most successful treatment, followed by Scenario Three (two gout flares, each reaching a maximum pain of five and each lasting one week long) by eight (37%) participants, and Scenario Two (a gout flare which reaches a maximum pain of five and lasts two weeks long) by 3 (14%) participants. Participants commented on flare duration, pain severity, and flare frequency when considering which gout flare scenario was most indicative of successful treatment.

Illustrative quotes are shown in **Table 2**.

Duration

The duration of the flare was the most commonly mentioned attribute considered by patients who perceived Scenario One as being most indicative of successful treatment, despite having a maximum pain severity score of ten: “Although the pain is more severe, it only lasts one

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week, rather than having a mild [one that] lasts longer. ... It's probably better having a gout flare for a short amount of time rather than ongoing." (Patient 19, M, 30 years). The idea of a gout flare being ongoing and lingering was a key concern for patients, who preferred to get it "over and done with", even if it meant they would get another flare later on (Scenario Three). A shorter flare duration was also considered important to treatment success, because flares of longer duration meant some participants had to take more time off work.

Pain severity

The lower severity of gout flare pain in Scenarios Two and Three was the most important attribute for patients who perceived these Scenarios as being most indicative of treatment success over Scenario One, which had a higher pain severity. A gout flare with less pain severity was considered more manageable by some patients, even if it was of a longer duration: "I would rather have one that's not so severe, lasting a little bit longer – you know, you can sort of manage it" (Patient 8, M, 44 years). Less severe pain allowed participants to engage in a greater level of function and undertake some activities which they would have difficulty with if the pain was more severe. For one patient a flare with severe pain impacted his ability to work "You know, 'cause working at the prison, I was driving a truck - well, I can't drive [with a severe flare]" (Patient 8, M, 44 years).

Frequency

The single flares in Scenarios One and Two were considered a more successful outcome than multiple flares: "I'd rather deal with it once, you know-yep. I'd rather deal with it once and then be gone with it" (Patient 14, M, 60 years). One patient also commented that if a treatment was successful "the time between the flare-ups would become longer and longer"

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(Patient 14, M, 60). Having a second flare after a period of no flares also made patients frustrated and feel that the treatment was not working.

DISCUSSION

This study investigated factors associated with gout flares which are perceived by patients with gout to be the most indicative of successful treatment. Flare duration, flare frequency and pain severity all influenced how patients perceived treatment success. Although these factors are inter-related, flare duration appeared to be an important factor when patients were considering treatment efficacy.

Some patients were willing to experience more severe pain, such as a pain score of 10 compared to a pain score of 5, if the duration of the flare was shorter. A recurrent idea highlighted among patients in the current study was the notion of not wanting to deal with the flare for any longer than they had to. The main reasons behind this were the impact that flare duration had on the individual's ability to work, socialize and even carry out simple tasks around the home. Flare duration is rarely measured and reported in long term gout studies [7], and reporting methods are inconsistent; with authors reporting either the mean duration of individual flares or the total number of gout flare days over the follow up period.

In the current study, patients selected scenarios with single flares as indicative of treatment success, over those with multiple flares, suggesting the frequency of flares does play a role in whether patients perceive treatment to be working. This finding is consistent with existing qualitative research in which more frequent flares have a greater impact on work life and taking days off work, psychological wellbeing and ability to plan in advance [3]. A quantitative survey of 1100 people with gout also reported a reduction in perceived treatment satisfaction as the number of flares increased [12]. However, two thirds of patients who

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experienced five or more flares in the previous year also reported satisfaction with treatment [12], highlighting the importance of factors other than flare frequency that may be driving patient perceived treatment efficacy.

Pain severity appeared to be the least influential of the three factors perceived as indicative of treatment efficacy. Pain severity is a dominant theme in the overall patient experience of gout [2, 3] and is recommended by OMERACT as a mandatory outcome measure for both acute studies of gout flares and studies investigating the long-term management of gout [4]. The current findings suggest that a reduction in flare pain severity alone may not be as important to patients with gout when thinking about treatment success, without also considering the duration and frequency of the flares.

This study explored the patient perspective on what factors influence treatment efficacy; however, there are limitations with the study. Firstly, although the three flare scenarios were based on data collected from patient flare diaries [6], patient consumers were not directly involved in the design of the scenarios. In addition, although the sample size was small with only 22 participants, this was a qualitative study in which recruitment and analysis occurred simultaneously; with qualitative experts stating new information is rarely generated after interviewing 20 participants [12]. The majority of these participants were New Zealand European middle-aged males and despite these findings aligning with the trends in gout prevalence, this may reduce generalizability of the findings to people with gout of non-European ethnicity. The influence of participant characteristics (including gender) and disease characteristics (including flare history and comorbidities) on patient perceived treatment efficacy was also not examined as part of this study; it therefore remains unknown whether such factors play a role. Furthermore, all participants in this study were recruited from databases of patients with gout who had participated in previous research, including trials of urate lowering therapy, which may have influenced their perceptions of the

importance of the flare characteristics examined in the current study. Additionally, this study only investigated the influence of pain severity, duration and frequency. Other factors not assessed in the current study, including activity limitation, have also been shown to be important to the burden of flares [2, 3] and may have influenced the perception of treatment success. Finally, it remains unclear whether factors related to an individual flare (i.e., the worst flare) or the cumulative impact of flares over time has greater importance to patients when considering treatment efficacy. Further research is required to address these points in order to develop a standardised tool that comprehensively and consistently captures the burden of gout flares over time.

This study provides a number of novel observations. Firstly, we have shown that flare duration is the most important factor when patients are considering treatment efficacy. In addition, pain severity, although important, was the least influential of the three factors in patients' perceptions of treatment success. This is a novel finding and suggests that patients prefer to have flares of shorter duration and less frequency, rather than less pain. Considering that flare duration is not routinely measured in long term studies of gout, these findings have important implications for future research. Furthermore, these insights will be valuable when developing a standardised tool for capturing flare burden over time in long term studies of flare prevention.

In conclusion, this study highlights the inter-related factors of flare duration, flare frequency and pain severity, which are all considered by patients when thinking about treatment efficacy over time. Long term studies of gout should ideally capture all of these factors to better represent patients' perceptions of treatment success.

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FIGURE LEGENDS

Figure 1. Visual representations of the three gout flare scenarios over a hypothetical 6-month period.

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Table 1. Participant demographic and clinical characteristics (n = 22)

| | |
|--|-------------------------------|
| Gender, n (%) | |
| Male | 17 (77%) |
| Female | 5 (23%) |
| Age in years, median (range) | |
| | 67 (27-84) |
| Ethnicity, n (%) | |
| NZ European | 12 (55%) |
| Māori | 5 (23%) |
| Asian | 3 (14%) |
| Pacific Peoples | 2 (9%) |
| Disease duration, mean (range) | |
| | 11 years (6 months -35 years) |
| Current urate lowering therapy | |
| | 20 (91%) |
| Age at onset of gout in years, mean (range) | |
| | 49 (20-81) |
| Number of flares in the last 6 months, n (%) | |
| 1-4 | 16 (73%) |
| 5-9 | 2 (9%) |
| ≥10 | 4 (18%) |

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Table 2. Illustrative quotes indicating flare attributes considered indicative of treatment success

| | |
|-----------------------|---|
| Pain severity | “A pain score of five is manageable, and for two weeks.” [Patient 3, M, 59 years] |
| | “You’ve got two independent flares, each lasting a week and it’s only at five—well, it’s better than a week of ten, I can assure you.” [Patient 10, M, 73 years] |
| | “If I compare five and ten—a pain of five compared to what I reckon was a ten, I could sit around and probably do a lot of things I couldn’t do with [a pain of ten].” [Patient 10, M, 73 years] |
| | “I would rather have one that’s not so severe, lasting a little bit longer – you know, you can sort of manage it” [Patient 8, M, 44 years]. |
| Flare duration | “You can’t have so much time off work, you know, so I’d rather have [an] intense [flare] lasting a shorter time.” [Patient 8, M, 44 years] |
| | “Two weeks to recover just sounds horrible. (..) I’d rather have a shorter, sharper pain at the beginning, and then have it go away faster, than have it linger for two weeks.” [Patient 12, M, 48 years] |
| | “I’d prefer to get it over and done within a week, and if it means I’m still going to get another one, I’ll put up with that rather than having it for two weeks.” [Patient 1, M, 74 years] |
| | “A gout flare that lasts for two weeks is about, um, thirteen days too long”. [Patient 1, M, 74 years]. |
| Frequency | “Because it’s just one flare-up... I wouldn’t want two gout flares.” [Patient 3, M, 59 years] |
| | I think I would know the medication is working, if maybe I had a flare of once a week, and then its only once a month, and then maybe for three months, nothing. [Patient 4, M, 59 years] |
| | “Psychologically, you feel like you’ve actually got rid of it, then it comes back again. And so, I think that’s quite frustrating... you feel like you’ve healed |

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Visual representations of the three gout flare scenarios over a hypothetical 6-month period.