RHEUMATOLOGY

Concise report

Long-term persistence and adherence on urate-lowering treatment can be maintained in primary care—5-year follow-up of a proof-of-concept study

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Abstract

Objectives. To evaluate the persistence and adherence on urate-lowering treatment (ULT) in primary care 5 years after an initial nurse-led treatment of gout.

Methods. One hundred gout patients initiated on up-titrated ULT between March and July 2010 were sent a questionnaire that elicited information on current ULT, reasons for discontinuation of ULT if applicable, medication adherence and generic and disease-specific quality-of-life measures in 2015. They were invited for one visit at which height and weight were measured and blood was collected for serum uric acid measurement.

Results. Seventy-five patients, mean age 68.13 years (s.d. 10.07) and disease duration 19.44 years (s.d. 13), returned completed questionnaires. The 5-year persistence on ULT was 90.7% (95% CI 81.4, 91.6) and 85.3% of responders self-reported taking ULT $\geqslant 6$ days/week. Of the 65 patients who attended the study visit, the mean serum uric acid was 292.8 μmol/l (s.d. 97.2).

Conclusion. An initial treatment that includes individualized patient education and involvement in treatment decisions results in excellent adherence and persistence on ULT >4 years after the responsibility of treatment is taken over by the patient's general practitioner, suggesting that this model of gout management should be widely adopted.

Key words: gout, urate lowering treatment, persistence, adherence

CLINICAL SCIENCE

Rheumatology key messages

- Excellent long-term persistence and adherence on urate-lowering treatment can be achieved with patient education in gout.
- The benefits of individualized patient education for gout treatment persists in the long term.

Introduction

Gout is the most common inflammatory arthritis, with a prevalence of 2.5% [1]. Although curable, its management is suboptimal, as evidenced by low urate-lowering treatment (ULT) initiation rates even in people who consult their general practitioner (GP) for gout and fulfil the recommended criteria for ULT [1, 2]. Moreover, the persistence and adherence on ULT is generally poor [1, 3, 4]. For example, half of all men and women discontinued ULT by 358 and 379 days, respectively, in a community-based study, while another study reported the 12-month persistence on ULT to be even lower, at 22.6% [4, 5]. Adherence to ULT ranges from 10 to 46% and is lower than medication adherence in other chronic illnesses, including RA [1, 3, 4, 6, 7]. In the UK, only 34–38% of gout patients get initiated on ULT, and of these, only 39% are adherent to ULT at 12 months [1, 2].

A proof-of-concept study from Nottingham, UK demonstrated that a predominantly nurse-led treatment package

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consisting of individually tailored patient information regarding gout and its management and initiation and upward dose titration of ULT as per the British Society for Rheumatology (BSR) recommendations resulted in 92% of gout patients persisting on ULT at 1 year [8]. However, whether these patients would persist on ULT in a real-world setting, in the long-term, once the responsibility of prescribing ULT is taken over by the patient's own doctor at the end of the 12-month study period is not known.

Thus the overall aim of this study was to explore the effects of an initial nurse-led gout treatment program on ULT continuation in the long-term. The specific objectives were to examine the persistence and adherence on ULT and to calculate the proportion of patients who meet the BSR and EULAR treatment target for serum uric acid (SUA) at 5 years [9].

Methods

Study design

This was a cross-sectional study investigating persistence and adherence on ULT in a primary care setting. Crystal-proven gout patients, recruited between March and July 2010, previously participated in the proof-of-concept study, with the last study visit in July 2011 [8].

Recruitment

One hundred of the 106 gout cases (5 died, 1 moved out of the area) were sent a postal questionnaire in September 2015. The questionnaire elicited information about demographic characteristics, current ULT, reason(s) for ULT discontinuation (if applicable), self-reported adherence to ULT and quality of life assessed by the 36-item Short Form Health Survey version 2 (SF-36v2) and the Gout Impact Scale (GIS) of the Gout Assessment Questionnaire version 2 [10, 11]. Responders were invited to attend a hospital visit at which height, weight and blood pressure were measured and blood was collected for SUA measurement. Data on SUA and serum creatinine measurements requested by GPs between July 2011 and September 2015 were obtained from the Clinical Chemistry Department, Nottingham University Hospitals National Health Service (NHS) Trust.

The postcode of each study participant was used to obtain their Index of Multiple Deprivation (IMD), a composite measure of socio-economic and health care deprivation, from the Department for Communities and Local Government, England. The IMD ranks each postcode ($n = 32\,844$) in England according to their relative deprivation, with lower ranks being the most deprived. This study was approved by the Medical School Ethics Committee, University of Nottingham, UK (Ref: B18062015 SoM ROD). All study participants gave informed consent for participation in this study.

Statistical analysis

The descriptive statistics used in this study were number (%) and mean (s.d.). Persistence and adherence rates and their 95% CIs were calculated. Independent sample t test and chi-square test were used to compare the baseline disease and demographic characteristics of questionnaire responders and non-responders. The SF-36v2 scores were standardized using population norms generated from a large UK community sample [11]. Scores of each domain of SF-36v2 at baseline and at the 5 year follow-up were compared using paired t test. The odds ratio (OR) and 95% CI were used to examine associations. Binary logistic regression was used to calculate the OR. All statistical analyses were carried out using STATA (StataCorp, College Station, TX, USA). *P*-values $\leqslant 0.05$ were considered statistically significant.

Results

Seventy-five of the 100 questionnaires were returned and 65 patients attended the study visit. The mean age, disease duration and BMI were 68.13 years (s.d. 10.07), 19.44 years (s.d. 13) and 31.12 kg/m^2 (s.d. 4.51), respectively. Twelve per cent of responders were women and 14.7% had tophaceous gout. Questionnaire responders were older than non-responders at the baseline visit in 2010 (Table 1). However, this was not statistically significant and other disease and demographic characteristics, including SF-36 scores and IMD, were comparable between the two groups (Table 1).

Sixty-eight of the 75 responders were on ULT at the time of the follow-up questionnaire, giving a persistence of 90.7% (95% CI 81.4, 91.6). The reasons for discontinuing ULT were: felt to be no longer required (3 patients), fed up with taking ULT (2), temporary discontinuation for unrelated reasons (1) and reason unclear (1). The 5-year persistence was comparable in those on allopurinol (93.1%), febuxostat (81.8%) and benzbromarone (100%) (*P* = 0.47). The dose of ULT was reduced in 11 participants [allopurinol 400–300 mg/day (*n* = 9) and 500–400 mg/day (*n* = 1), febuxostat 120–80 mg/day (*n* = 1)], remained the same in 52 participants and was increased in 3 participants. Two participants were commenced on a different ULT. A median of 1 [interquartile range (IQR) 0–3] SUA measurement and 4 (IQR 2–7) serum creatinine measurements were requested by the GPs between the end of the proof-of-concept study and September 2015, and only 37.5% patients had $\geqslant 2$ SUA measurements during this period.

Of responders, 85.3% (IQR 74.4–92.0) self-reported taking ULT on $\geqslant 6$ days in an average week (Fig. 1A). The mean SUA at the 5 year visit was 292.8 µmol/l (s.d. 97.2). The SUA was significantly lower in those on ULT than in those not on ULT [mean SUA 269.4 µmol/l (s.d. 50.4) *vs* 577.2 (63.6); *P* < 0.001]. Of the patients for whom the 5 year SUA levels were available, 86.4% (95% CI 75.5, 92.9) had an SUA $\leqslant 360$ µmol/l and 69.7% had an SUA $\leqslant 300$ µmol/l. Those who self-reported forgetting ULT on $\geqslant 2$ days/week were significantly less likely to have an SUA $\leqslant 300$ µmol/l [OR 0.19 (95% CI 0.04, 0.84); *P* = 0.029] (Fig. 1B).

The bodily pain domain score of SF-36v2 improved over 5 years, with mean baseline and 5 year scores of 42.55

TABLE 1 Disease and demographic characteristics at the start of the proof-of-concept study

Characteristic	Questionnaires returned (n = 75)	No response or not mailed (n = 31)	P-value
Age, mean (s.d.), years	62.2 (10.1)	57.6 (13.2)	0.06
Sex, female, %	12	9.7	0.73
BMI, mean (s.d.), kg/m^2	31.1 (4.5)	30.2 (5.2)	0.34
Age at first attack, mean (s.d.), years	48.7 (15)	43.5 (16.7)	0.12
Number of attacks in 12 months, mean (s.d.)	3.8 (3.6)	4.3 (3.0)	0.52
Tophi present, %	14.7	19.4	0.55
Serum uric acid, mean (s.d.), µmol/l	456.6 (11.4)	453.6 (18.6)	0.88
SF-36v2 domain scores, mean (s.d.)			
Physical function	41.4 (14.1)	40.8 (15.3)	0.80
Role physical	44.0 (12.9)	43.7 (13.0)	0.93
Bodily pain	42.5 (10.5)	44.4 (13.2)	0.44
General health	44.4 (11.1)	43.6 (12.1)	0.74
Vitality	51.4 (10.6)	47.4 (12.5)	0.10
Social functioning	49.3 (10.8)	48.7 (12.0)	0.81
Role emotional	49.1 (11.7)	46.2 (12.4)	0.25
Mental health	53.3 (9.5)	49.5 (13.1)	0.10
Index of multiple deprivation rank, media (IQR)	6 (3–8)	5 (3–7)	0.33

FIG. 1 Adherence on urate lowering treatment (ULT) and its effects on serum uric acid (SUA)
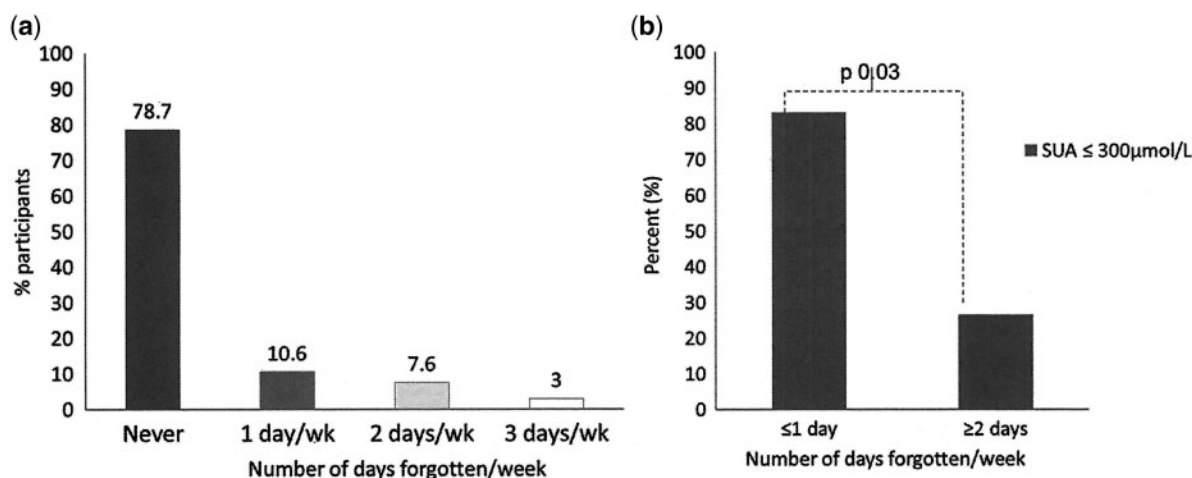
(A) Proportion of study participants who forget taking ULT in an average week, and (B) Proportion of study participants meeting treatment target for SUA.

(s.d. 10.47) and 46.01 (s.d. 11.32), respectively, a mean improvement of 3.46 (95% CI 0.69, 6.23) (P = 0.015). There were no statistically significant differences in the other SF-36v2 domain scores over 5 years (data not shown). Similarly, study participants had excellent scores on each of the five GIS domains and in the overall GIS score. The mean (95% CI) gout concern overall, gout medication side effects, unmet gout treatment need, well-being during attack and gout concern during attack were 34.88 (28.51, 41.25), 37.84 (32.15, 43.53), 22.30 (17.98, 26.62), 40.47 (34.75, 46.19) and 32.42 (27.34, 37.47), respectively.

Discussion

This study examined the effects of a 1 year initial nurse-led treatment of gout on long-term persistence and adherence to ULT after the responsibility for prescribing ULT was handed over to the patients' own doctor. It reports that >90% of patients persisted on ULT at 5 years with excellent adherence and that >86% of patients met the EULAR treatment target for SUA at 5 years. These findings suggest that a personalized interactive education about gout and full involvement of patients in management decisions results in improved long-term persistence on ULT

even after the responsibility of prescribing ULT is handed over to the patients' own GP. This concurs with the findings of a systematic review that concluded that patient education improves medication adherence [12]. As reported previously, three of the six patients who discontinued ULT did so because they felt that long-term ULT was no longer necessary [13, 14]. These findings suggest that the need for long-term ULT should be reinforced periodically.

In a cross-sectional study from New Zealand, patients' determination to maintain a normal SUA was the only psychological determinant of treatment success [15]. It is possible that the individualized patient education during the proof-of-concept study increased their commitment to reduce the SUA to below treatment target and that progressive reductions in SUA during treat-to-target ULT provided the requisite positive feedback to maintain this. Thus the key components that resulted in excellent 5 year persistence on ULT are an experienced rheumatologist with an interest and expertise in gout (M.D.) fully assessing the patient and providing initial explanations concerning gout, its possible effects and available treatment options; nurse-led disease monitoring and ULT dose escalation and reinforcement of patient education over the first year and subsequent continued prescription of ULT by the GP. Although not directly measured, it is likely that the excellent adherence to ULT is at least due in part to ongoing follow-up and encouragement to adhere to ULT by the GP.

In keeping with the findings of a previous study, we found that poor adherence to ULT associated with high SUA [16]. This study also shows that long-term ULT improves bodily pain in gout. The magnitude of improvement in our study is smaller than that reported previously in studies undertaken predominantly in patients from secondary care [17], and this may be due to participants in the other studies having more severe disease, resulting in a greater improvement in quality of life with ULT. Similarly, the scores on gout concern overall, unmet gout treatment need and gout concern during an attack domains of the GIS in this well-treated gout cohort are 25.9–44.7%, 20.9–41.6% and 35.5–40.8% lower, respectively, than those observed in other gout cohorts, providing further evidence of long-term beneficial effects from an initial nurse-led treatment of gout [18–20]. Smaller differences were present in the gout medication side effects (13.3–21.7%) and well-being during attack (14.2–7.4%) domains [18–20] (Supplementary Fig. S1, available at *Rheumatology* Online).

There are several strengths of this study, namely, a very high response rate to the questionnaire and long follow-up period. However, there are several caveats to this study. First, we do not have information about persistence and adherence on ULT in those who did not respond to the follow-up questionnaire. Additionally, the questionnaire non-responders were 4.6 years younger than responders. Since persistence on ULT is lower in the younger age group, it is possible that the overall long-term adherence and persistence on ULT in the proof-of-concept study

participants is lower than that estimated in this study. Similarly, non-responders had slightly worse disease at baseline, which could relate to socio-economic deprivation, which associates with reduced medication adherence. However, responders and non-responders had similar socio-economic deprivation scores (Table 1). Nevertheless, even if all non-responders are assumed to be not taking ULT, the 5 year persistence on ULT would be 68%. Even this is much better than other reports of long-term persistence on ULT. Unfortunately we did not collect information on the GIS during the proof-of-concept study in 2010–11 and are unable to measure any long-term improvements in disease-specific quality of life from the initial nurse-led package of care. Due to the small sample size and high persistence and adherence rates, we did not perform multivariate analysis to identify the disease and demographic predictors of non-persistence or non-adherence to ULT, as any such analysis would be prone to type II error. Additionally, we did not collect data on the number of times a patient was seen by his/her GP for gout between the final study visit in 2011 and the questionnaire survey in 2015. These data are likely to be inaccurate when captured retrospectively in a questionnaire survey after 4 years since a review of gout would have been part of a broader periodic medical review and the patient may not remember being asked about it several years later.

In conclusion, this study demonstrates that an initial package of care that includes individualized education, patient involvement in management decisions and a treat-to-target approach to ULT results in the best long-term ULT adherence and persistence reported thus far. Such treatment may be initiated by a suitably trained nurse or by any other allied health care professional, such as a community pharmacist. Further research is required to determine if persistence and adherence to long-term ULT are due to retained knowledge of gout and its treatment and if such treatment improves renal function and reduces the risk of cardiovascular disease.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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