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Clinical science

Non-adherence to urate lowering therapy in gout after 5 years is related to poor outcomes: results from the NOR-Gout study

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Abstract

Objectives: Patients with gout need to adhere to medication over time to achieve good outcomes. We assessed self-reported adherence to medication with urate lowering therapy (ULT) 5 years after a treat-to-target intervention and studied how non-adherence was related to baseline demographic and disease variables.

Methods: Patients in the NOR-Gout observational study were included after a recent gout flare and serum urate >360 μmol/l. Patients [mean age 56.2 (S.D. 13.6), 94.5% males, 17.2% with tophi] attended tight-control visits over one year with escalating urate lowering therapy using a treat-to-target strategy. Five-year follow-up included the Medication Adherence Report Scale (MARS-5) questionnaire (range 5–25) for adherence. Flares and SUA target achievement were compared for 5-year adherence to medication.

Results: At 5 years most of the 163 patients used ULT (95.1%). MARS-5 adherence scores after 5 years were high (median 24, interquartile range 22–25). Patients in the lowest MARS-5 quartile had, compared with the highest quartile, more often a flare during the last year of follow-up (33.3% *vs* 9.5%, $P = 0.004$) and reached the 5-yr serum urate treatment target less frequently (45.2% *vs* 87.5%, $P < 0.001$). Baseline lower age (OR 0.56, 95%CI 0.39–0.79), non-European origin (OR 0.22, 95%CI 0.06–0.80), lower SF-36 mental health scores (OR 0.94, 95%CI 0.91–0.98) and less joint pain during last flare (OR 0.73, 95%CI 0.58–0.92) were independent risk factors for non-adherence to medication.

Conclusions: Patients reported high adherence to medication after 5 years. Non-adherence was related to more flares and less urate target achievement. Younger age and non-European origin were associated with non-adherence.

Keywords: gout, non-adherence, adherence, treat to target, urate lowering treatment, outcome measures, health-related quality of life.

Rheumatology key messages

- Self-reported adherence to medication 5 years after a treat-to-target intervention is high in patients with gout.
- After 5 years people with non-adherence had more flares and lower achievement of the serum urate target.
- Risk factors for non-adherence to urate lowering treatment includes young age and non-European origin.

Introduction

Gout is a prevalent inflammatory joint disease, where hyperuricaemia leads to the formation of monosodium urate (MSU) crystals, followed by recurrent painful flares of inflammation [1]. To prevent future gout flares and reduced health-related quality of life during the patient's long-term disease course, urate lowering treatment (ULT) is recommended to reach target serum urate acid (sUA) levels [2, 3] also with the help of patient education [4].

However, patient adherence to prescribed long-term gout treatment is low and overall adherence was only 47% in a recent meta-analysis and may vary dependent on whether assessments are based on prescription, pill counts, self-report or interview [5]. Recently, only minor increases in the use of ULT in the UK have been seen since the early 2000s [6]. Further, many patients are not treated with ULT at all and thus do not reach target sUA levels [7–9].

Non-adherence is frequent and may translate to poor treatment outcomes. Adequate education during patient care may increase adherence [10] and empowerment of patients with active follow-up is associated with achieving the sUA treatment target [11]. Excellent adherence to ULT in gout was

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achieved in a 5-year follow-up study from Nottingham, UK [12].

We lack knowledge on how self-reported adherence among gout patients treated with ULT associates with long-term disease outcomes of flare and successful achievement of the sUA target. Further, we know little about whether demographic or clinical baseline variables can predict long-term non-adherence, giving the clinical care provider useful information.

A conceptual approach to adherence research describes adherence to medication with three components: initiation, implementation and discontinuation prescribed [13]. Both intentional and non-intentional adherence to medication can be assessed using the self-report Medical Adherence Scales (MARS) [14] or the Morisky Medication Adherence Scale [15], as compared with the Intentional Non-adherence Scale that measures intentional adherence alone [16].

Our hypothesis was that long-term non-adherence to ULT would be related to unfavourable outcomes in patients with gout, including a higher frequency of flares and less frequent achievement of the sUA target. Thus, we studied adherence in gout patients 5 years after a tight control, treat-to-target intervention in the first year and examined associations with baseline factors and gout outcomes.

Methods

Study design and participants

This study reports on patients completing a 5-year follow-up examination in the prospective observational NOR-Gout (Gout in Norway), which was performed in a hospital-based rheumatology clinic [17] to study long-term gout outcomes. All included patients had crystal proven gout and fulfilled the ACR/EULAR classification criteria for gout [18]. They had been recruited after a recent clinical gout flare at the rheumatology outpatient clinic and were, after indicating willingness to participate, pre-screened and consented to inclusion. They were required to have an increased sUA level >360 μmol/l at inclusion. In NOR-Gout they started ULT with allopurinol or febuxostat if intolerance to allopurinol [17] with frequent follow-up visits during the first year, met after 2 years and had a final visit at 5 years. During the treat-to-target strategy during year 1, ULT was escalated during monthly visits to achieve sUA <360 μmol/l (or <300 μmol/l if clinical tophi were present) as internationally recommended [2]. The starting dose of allopurinol was 100 mg daily, and 40 mg daily for febuxostat. In all patients starting ULT a prophylaxis of 0.5–1 mg with colchicine was prescribed for 3–6 months. The study (ACTRN12618001372279) was registered at https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=374171. The Norwegian Regional Committee for Medical and Health Research Ethics South East (reference number 2015/990) approved the study, patient representatives were included in the study planning and participants had given their written informed consent.

Demographic, clinical and laboratory assessments

During the first year all patients had frequent study visits with a nurse and/or a rheumatologist until the sUA target was achieved. Clinical follow-up examinations included joint counts, subcutaneous tophi assessments, laboratory analyses and questionnaires on health status.

At baseline, patients reported age, gender, ethnic origin, marital status, family history for gout, disease duration, highest level of education, smoking and alcohol consumption, and consumption of sugar-sweetened drinks.

In this study the main outcome variable was adherence to medication, which was measured after 5 years with MARS-5. The five-question version in MARS-5 was originally described by Horne [14], further validated [19] and translated into Norwegian [20]. Respondents indicate their degree of agreement with each individual statement of the five about medicines ('I forget to take my medicines', 'I change the dose of my medicines', 'I stop taking my medicines for a while at times', 'I decide not to take a dose' and 'I take less than I am instructed to'). Item responses are scored on a 5-point Likert scale where 1 = always, 2 = often, 3 = sometimes, 4 = rarely and 5 = never. Scores range from 5 to 25, with higher scores indicating higher adherence.

Information on number of flares 'ever' and 'during the last year' before the study was collected. Occurrence of flares was self-reported by patients during study visits and at 5 years during a structured interview with the study nurse who recorded flares for the last year.

Comorbidities were assessed by the Self-Administered Comorbidity Questionnaire (SCQ) at baseline (score range 0–36) [21], including 12 medical problems, allocating one point per problem including presence of the problem, receiving treatment and causing a functional limitation.

At all visits OMERACT-endorsed questionnaires on patient-reported outcomes [22] including joint pain, general pain and patient global assessment of disease activity on a 0–10 numerical rating scales were completed and also joint pain severity during the most recent and the strongest flare (0–10 numerical rating scales), with 0 = no pain and 10 = unbearable pain. Physical function was measured with the Health Assessment Questionnaire Disability Index (HAQ-DI) [23]. Health status was assessed by the Short-Form general health questionnaire (SF-36) [24], reporting physical and mental component summaries (0–100, 0 = worst). From SF-36, SF-6D utility was derived.

The Work Productivity and Activity Impairment Questionnaire (WPAI) [25] determines employment status during the past 7 days: with four separate scores on (i) the percentage of missed work (absenteeism); (ii) the percentage of impaired productivity while at work (presenteeism), such as how much impact the disease has on work productivity; (iii) overall work impairment, which combines absenteeism and presenteeism; and (iv) percentage of impairment of the disease on activities performed outside of work. Greater scores indicate greater impairment. Patients not working provided only data for the WPAI Activity impairment scale.

Clinical assessments included body mass index (BMI), 44 swollen and tender joint counts and subcutaneous tophi assessment. Laboratory examinations measured sUA (μmol/l), erythrocyte sedimentation rate (ESR) creatinine and estimated glomerular filtration rate (eGFR) using the CKD-EPI Creatinine Equation.

To assess by imaging the baseline level of crystal deposition in joints and tendons, all patients were examined by ultrasound and dual-energy computed tomography (DECT). The crystal burden in joints and tendons ultrasound was at baseline scored as previously described [26] (scoring 0–3 for double contour, tophi and aggregates) with calculation of total ultrasound sum scores. For DECT (General Electric Discovery GE CT750 HD, USA), bilateral forefeet and ankles images were acquired at 80 KW and 140 KV, processed with a GE AW server software with a two-material decomposition

algorithm, which colour codes urate depositions using threshold values. DECT images were scored using a semiquantitative method as 0–3 [27], providing a sum score for the four regions (first metatarsophalangeal joint, other joints of the toes, ankles and midfeet, and tendons).

Statistics

Data were summarized using standard descriptive statistics. Between-group comparisons of continuous variables were done using two-sample *t* test and Mann–Whitney *U* tests as appropriate. Categorical data analyses applied the χ^2 test or Fisher's exact.

Adherence scores were divided into quartiles (MARS-5 scores ≤21, 22–23, 24 and 25). Non-adherence was defined as having a MARS-5 score of 21 or lower – the lowest quartile. Analyses of adherence were also performed for patients with at least median adherence scores (MARS-5 ≥ 24).

To identify potential variables associated with non-adherence, candidate variables were univariately tested for association with non-adherence. We considered the following demographic and clinical variables: age, gender, origin, disease duration, comorbidities (SCQ), education, BMI, smoking, alcohol use, physical activity, baseline ESR, sUA, eGFR at baseline, presence of subcutaneous tophi, experience of flares before the study or during year 1, tender and swollen joints, pain strength during the last and during the strongest flare ever, HAQ-DI, SF-36 physical and mental summary components and ultrasound and DECT scores.

Variables displaying $P < 0.25$ were then included in multivariable logistic regression models and successively removed to explore baseline predictors of non-adherence. We performed sensitivity analyses with other cutoffs for MARS-5 scores for the definition of non-adherence and adherence.

No adjustments were made for missing data. Analyses were performed with IBM SPSS statistics (version 29).

Results

Study population

The patient flow in the study is shown in Supplementary Fig. S1, available at *Rheumatology* online. Characteristics of 163 completers at 5 years are presented in Table 1. Patients were predominantly males, had at baseline a mean age of 56.2 (S.D. 13.6) years and a disease duration of 8 (S.D. 7.6) years. Fourteen of 17 non-European patients were of Asian origin with a mean age of 46.6 (S.D. 11.8) years.

At 5 years sUA was mean (S.D.) 338 (81) μmol/l, the treatment target (<360 μmol/l) was achieved in 71.0% (115/162) and 16.0% (26/163) of patients reported a gout flare during the past year.

Adherence

Use of ULT was reported by 95.1% (155/163) of patients with either allopurinol or febuxostat (Table 1). Mean (S.D.) MARS-5 score was high with 22.2 (3.1) ranging from 15 to 25, with a high median of 24 out of maximum 25. Non-adherence comprised patients in the lowest quartile with MARS-5 score ≤21 (42/158, 26.6%). High adherence with perfect MARS-5 adherence scores (25 out of 25) was seen in 20.3%, corresponding to the highest quartile.

Fig. 1 shows the responses to the five MARS-5 questions. Patients report high levels of intentional adherence in the first four questions, but lower unintentional adherence in the last question.

Table 1. Patient characteristics at baseline and during the study

	n	% or mean (S.D.)
Age (years)	163	56.2 (13.6)
Male	154/163	94.5%
European origin	140/157	89.2%
Disease duration (years)	159	8.1 (7.6)
College education	100/160	62.5%
Working	110/161	68.3%
Body mass index (kg/m^2)	163	28.8 (4.5)
Co-morbidity score (SCQ)	162	3.7 (3.2)
Subcutaneous tophus	28/163	17.2%
Smoking daily	12/171	7.5%
Alcohol use at least weekly	97/160	60.6%
Physical activity at least 3 times/week	55/160	34.4%
Allopurinol use ever at baseline	22/150	14.7%
Allopurinol use year 5	132/163	81.0%
Allopurinol dose (mg daily)		262 (111)
Febuxostat use year 5	23/163	14.1%)
Febuxostat dose (mg daily)		57 (20)
Erythrocyte sedimentation rate (mm/h)	154	13.0 (12.4)
Serum urate (μmol/L)	163	495 (70)
Strongest joint pain ever (0–10)	161	8.2 (1.5)
Flare during year 1	134/163	82.2%
Health assessment questionnaire (0–3)	161	0.33 (0.55)
Work productivity and activity index		
% Work missed	102	5 (17)
% Impairment at work	99	18 (28)
% Overall work impairment	100	20 (30)
% Activity impairment	155	29 (31)
Ultrasound sum score	162	18.7 (12.4)
Dual energy computed tomography sum score	155	4.5 (6.3)

SCQ: Self-Administered Comorbidity Questionnaire.

Association between non-adherence and 5-year disease outcomes (sUA treatment target achievement and flare)

At 5 years follow-up, more flares in the preceding year were reported with 33.3% in the lowest as compared with 9.4% in the highest adherence quartile ($P = 0.004$). Likewise, the sUA treatment target achievement was lower in the lowest MARS-5 category, with only 45.2% of the patients with non-adherence achieving target, increasing to 87.5% in the highest adherence quartile ($P = 0.001$) (Fig. 2).

Non-adherence and baseline demographic and disease characteristics

Table 2 shows baseline demographic and disease variables in patients with non-adherence to medication (MARS-5 ≤ 21) as compared with patients with higher adherence scores. Patients with non-adherence had at baseline lower age, were less likely to report European origin, had worse SF-36 mental scores, lower SF-6D utility scores and worse work impairment scores. Conversely, sensitivity analyses demonstrated that patients with at least median adherence (MARS score 24) or perfect MARS-5 scores of 25 correspondingly were of higher age, more frequently of European origin, had fewer flares before the study inclusion, and higher SF-6D utility than those with lower adherence (Supplementary Table S1, available at *Rheumatology* online). Imaging scores at baseline were not associated with non-adherence.

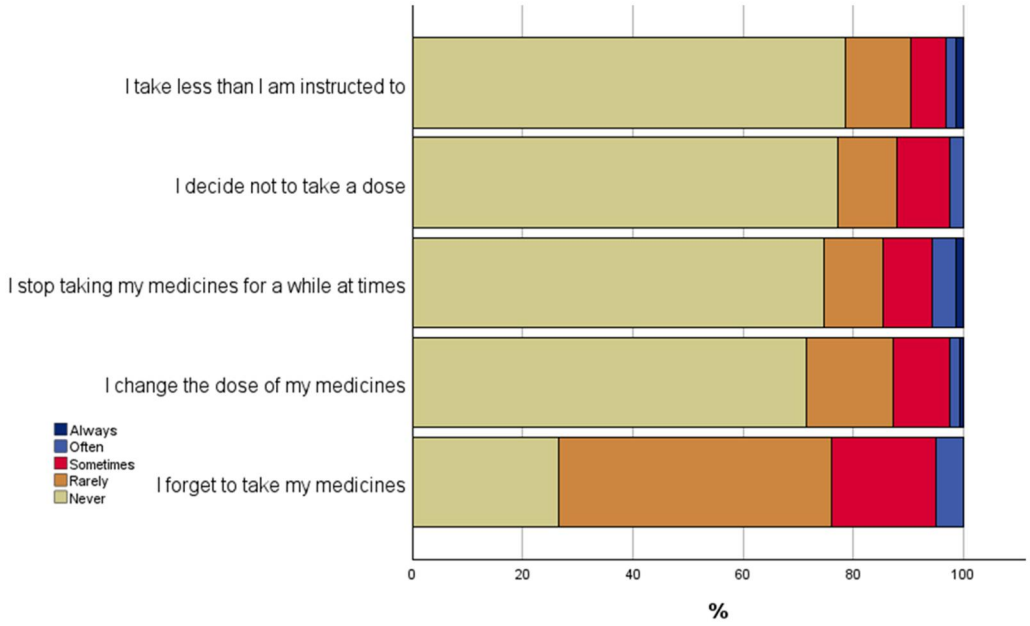

Figure 1. Responses to the five MARS-5 questions

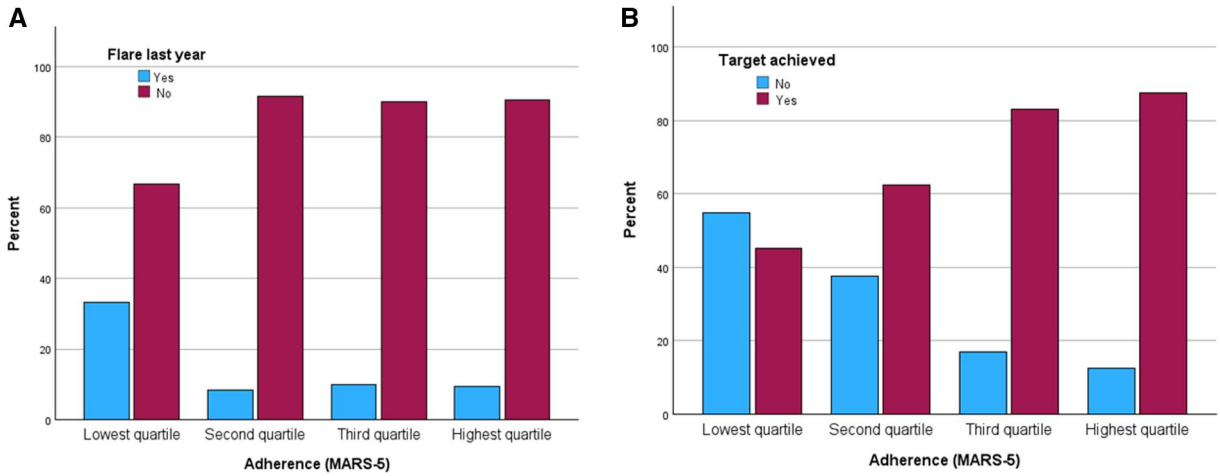

Figure 2. Flares and treatment target in adherence quartiles. **A** Gout flare occurrence last year according to MARS-5 quartiles after 5 years follow-up. $P = 0.004$ χ^2. **B** Achievement of serum urate target <360 µmol/L according to MARS-5 quartiles after 5 years follow-up. $P = < 0.001$ χ^2

Association of outcomes with non-adherence at baseline, 1 and 5 years

Table 3 demonstrates how outcomes with flares, achieved serum urate target and tophi compared at the different time points between non-adherent and adherent patients, and also includes kidney function and WPAI results. Flares and achieved SUA target over 5 years were related to non-adherence. For tophi there was a numeric reduction until 5 years in both groups, but with no statistically significant differences between adherence groups. Kidney function was maintained over 5 years in both groups.

Table 4 presents the univariate and the final logistic regression model for the risk of non-adherence, adjusting in addition the final model for gender. Lower age (OR 0.56 per 10 years increase), non-European origin (OR 0.22) and worse SF-36 mental (=low scores) scores (OR 0.94), were independently associated with non-adherence. In addition, higher activity impairment (impairment outside work due to the disease, OR 1.02) and less joint pain during the last flare (OR 0.73) emerged as risk factors of non-adherence in the final model.

Discussion

In our study of non-adherence to ULT at 5-year follow-up we found that almost all patients stated use of ULT and reported high self-report medical adherence in MARS-5. Patients with non-adherence had poorer outcomes with more frequent flares during the past year and lower attainment of the sUA target. We identified lower age, non-European origin, worse

Table 2. Baseline characteristics for patients with non-adherence *vs* higher adherence at 5 years with mean (S.D.) or %

	5-year follow-up (N = 158)		
	Non-adherence (MARS-5 ≤ 21) N = 42	Adherence (MARS-5 ≥ 22) N = 116	*P*-value
Age (years), mean (S.D.)	49.3 (13.8)	58.7 (12.5)	**<0.001**
Male (%)	97.6%	93.1%	0.45
European origin (%)	74.4%	95.6%	**<0.001**
Disease duration (years), mean (S.D.)	8.3 (6.8)	8.1 (8.0)	0.89
College education (%)	52.5%	65.5%	0.14
Married/cohabiting (%)	75.0%	73.9%	0.99
Working (%)	77.5%	65.5%	0.16
Body mass index (kg/m^2), mean (S.D.)	29.4 (4.9)	28.7 (4.5)	0.41
Co-morbidities (SCQ sum), mean (S.D.)	3.0 (3.0)	4.0 (3.3)	0.08
Physical activity ≥3 times weekly, *n* (%)	45.5%	32.2%	0.09
Smoking daily (%)	5.0%	7.8%	0.54
Alcohol consumption at least weekly (%)	50.0%	65.2%	0.09
Sugar-sweetened drinks daily (%)	50.0%	35.7%	0.11
Allopurinol use ever (%)	11.9%	11.2%	0.90
Serum urate (μmol/L), mean (S.D.)	511 (82)	490 (64)	0.09
Erythrocyte sedimentation rate (mm/h), mean (S.D.)	13 (12)	13 (12)	0.85
Creatinine (μmol/L), mean (S.D.)	96 (17)	95 (18)	0.72
eGFR (ml/min. per 1.73 m^2), mean (S.D.)	82 (18)	77 (18)	0.13
Previous flares >5 (%)	55.0%	50.9%	0.65
Joint pain last flare (0–10), mean (S.D.)	6.8 (2.0)	7.2 (1.9)	0.24
Number of flares first year, mean (S.D.)	3.1 (3.6)	2.6 (2.3)	0.27
Swollen joint present (at least 1) (%)	29.3%	32.2%	0.73
Tender joint (at least 1) (%)	48.8%	48.7%	0.99
Health assessment questionnaire (0–3), mean (S.D.)	0.47 (0.65)	0.27 (0.49)	0.08
SF-36 physical component summary (0–100), mean (S.D.)	40 (10)	39 (11)	0.39
SF-36 mental component summary (0–100), mean (S.D.)	47 (11)	52 (9)	**0.008**
SF-6D, mean (S.D.)	0.68 (0.13)	0.74 (0.15)	**0.041**
Work productivity and activity index			
% Work missed (%)	10 (23)	3 (14)	0.10
% Impairment at work (%)	31 (32)	13 (25)	**0.004**
% Overall work impairment (%)	37 (34)	14 (26)	**0.002**
% Activity impairment (%)	36 (30)	26 (32)	0.08
Ultrasound sum score, mean (S.D.)	18.2 (11.5)	19.1 (12.9)	0.67
Dual energy computed tomography sum score, mean (S.D.)	4.3 (6.0)	4.6 (6.4)	0.77

eGFR: electronic glomerular filtration rate; MARS-5: Medication Adherence Report Scale-5; SCQ: Self-Administered Comorbidity Questionnaire; SF-36: Short-form 36; SF-6D: Short-form 36 with 6 dimensions. Statistically significant *P*-values are given in bold.

mental health, higher WPAI impairment during activities outside work, and lower pain intensity during the last flare before baseline as factors associated with non-adherence.

Drug adherence to ULT is especially high when patients are empowered [11, 12, 28–30]. Our results support that patients who had been followed with tight controls and with education during 1 year of ULT report good medical adherence in MARS-5, and further 95% were on ULT with either allopurinol or febuxostat. Patients with lower MARS-5 scores had poorer outcomes, reported more frequent gout flares, and attained the sUA target less frequently. These findings may inform interventions that support adherence in clinical practice; developing culturally safe interventions focusing on younger people with work disability may be particularly useful.

Our use of MARS-5 as a self-report instrument for adherence meets the need for a simple, reliable self-report questionnaire for adherence score in gout. Self-report may overestimate adherence [31]. Among three tested adherence measures, the modified MARS had previously demonstrated the best evidence of reliability and validity and ease of administration in persons with rheumatoid arthritis [32].

MARS-5 has previously been used in rheumatoid arthritis [33, 34] and is in this study for the first time applied in gout. The questionnaire was found useful for measuring adherence in inflammatory bowel disease [35]. MARS-5 was also validated for higher adherence associated with stronger beliefs in treatment necessity and lower treatment concerns [19, 36]. MARS-5 cutoffs for high adherence often have defined patients with different disease other than gout with above median scores, but included thresholds in the different diseases of all values from 20 [37], 22 [35], 23 [35, 38, 39], to 24 [34], and one study defined non-adherence with a cutoff of 23 [40]. Our interest was especially related to non-adherence, and we defined patients in the lowest quartile (MARS≤21) as non-adherent, thus denoting the patient group that would need special attention to support successful ULT. We also did sensitivity analyses for other cutoffs and for adherent patients with at least median (at least 24) and perfect MARS-5 scores of 25 with results pointing at the same factors.

Few studies report long-term results and adherence after consistent ULT in gout. A high persistence on ULT was reported among patients who had participated in a ULT escalation study and were interviewed by telephone after >6 years [30]. In that study most patients (82%) were still on ULT, and these had less frequently experienced flares during the past years than those not on ULT, and 58% were still at sUA

target. In another study with a 5-year follow-up of patients applying treat-to-target ULT, 85% reported taking ULT at least 6 out of 7 days per week and sUA was significantly lower in those on ULT [12]. One other study reported some decline in adherence for ULT from 71.8% at year one to 58.2 at 3 years [29].

Some factors which in our study showed a long-term relationship to adherence had also been described by others, such as higher age for high adherence or at gout onset [41–43], longer disease duration [41], more comorbidities [43], palpable tophi [41] and more frequent follow-up visits [41]. Interestingly, receiving healthcare as a person of non-white origin has been associated with non-adherence [43]. As the patient perspective is important for successful ULT [42], we had included an educational intervention for all our patients.

Thus, adherence to medication is complex and multidimensional, involving a combination of treatment-, patient- and physician-related factors as suggested [44, 45]. Our study adds evidence that MARS-5, a short self-report adherence instrument, in gout identifies patients with long-term non-compliance or compliance.

Strengths of our study are the considerable number of well characterized patients from clinical practice who could be followed over 5 years. We applied broad clinical assessment including relevant disease outcomes with flares and sUA target achievement.

Limitations apply. First, all patients were intensively treated with ULT with frequent controls and monthly escalation of ULT as long as necessary, and our findings are not necessarily valid for patients not receiving intensive ULT. We do not wish to overstretch our interpretation of the results and indicated the severity of the study population. Second, gout flares were patient-reported, as the validated criteria for flares [46] had not been published when our study was initiated. However, a possible flare could be discussed with the research nurse during the study visit. Third, the observational design of our study does not allow causal inference. Fourth, in our long-term follow-up, completers *vs* non-completers displayed some differences with indicators of higher socioeconomic and better health status as frequently seen in long-term observational studies; however, 77% (163/211) of all included patients met for the final examination, demonstrating a high completion rate. Finally, self-report of adherence has not been extensively studied in gout; as our study is the first to use MARS-5, results should thus be interpreted with care and validated in other studies.

Because not taking medication will lead to poorer gout outcomes, we sought to identify possible risk factors for non-adherence that could be addressed by health care providers. Also, self-report non-adherence to medication in long-term gout ULT had previously not been reported. Modalities with a positive effect on existing non-adherence should be studied more, including the effect of education and remote follow-up with electronic notification [28, 47].

In summary, adherence to medication was high in our study after 5 years, and non-adherence was related to poor gout outcomes. Findings underscore that caregivers should address variables associated with non-adherence early during

Table 3. Key outcomes at baseline and after 1 and 5 years with mean (S.D.) or %

	Non-adherence (MARS-5 ≤ 21) N = 42	Adherence (MARS-5 ≥ 22) N = 116	*P*-value
Flare			
Baseline flares last year ≥3, (%)	57.5%	52.6%	0.39
Year 1	85.7%	81.9%	0.57
Year 5	33.3%	9.5%	**<0.001**
Serum urate <360 µmol/L			
Baseline	0%	0%	NA
Year 1	71.4%	92.2%	**<0.001**
Year 5	45.2%	80.0%	**<0.001**
Subcutaneous tophus present (%)			
Baseline	14.3%	18.1%	0.57
Year 1	14.3%	8.6%	0.30
Year 5	8.6%	5.2%	0.47
eGFR (ml/min. per 1.73 m^2), mean (S.D.)			
Baseline	82 (18)	77 (18)	0.13
Year 1	84 (19)	78 (18)	0.07
Year 5	82 (23)	77 (20)	0.23
Work productivity and activity index			
% Work missed			
Baseline	10 (23)	3 (14)	0.10
Year 1	1 (2)	2 (12)	0.65
Year 5	4 (18)	0 (2)	0.28
% Impairment at work			
Baseline	31 (32)	13 (25)	**0.004**
Year 1	12 (22)	3 (8)	0.07
Year 5	9 (20)	2 (7)	0.05
% Overall work impairment			
Baseline	37 (34)	14 (26)	**0.002**
Year 1	13 (22)	5 (15)	0.14
Year 5	10 (25)	2 (7)	0.08
% Activity impairment			
Baseline	36 (30)	26 (32)	0.08
Year 1%	13 (22)	9 (18)	0.39
Year 5%	12 (22)	7 (16)	0.23

MARS-5: Medication Adherence Report Scale-5; eGFR: electronic glomerular filtration rate. Statistically significant *P*-values are given in bold.

Table 4. Baseline factors and risk of non-adherence 5 years after a treat-to-target approach using logistic regression analyses[a]

	Univariate OR (95% CI)	*P* value	Final model[b] OR (95% CI)	*P*-value
Age per (10 years increase)	0.58 (0.44-0.77)	<0.001	0.56 (0.39-0.79)	0.001
Non-European origin	0.13 (0.04-0.42)	<0.001	0.22 (0.06-0.80)	0.022
SF-36 Mental component summary (0-100)	0.96 (0.93-0.99)	0.007	0.94 (0.91-0.98)	0.003
WPAI questionnaire (%)	1.01 (0.999-1.02)	0.08	1.02 (1.00-1.03)	0.018
Pain at last flare (0-10)	0.99 (0.74-1.08)	0.24	0.73 (0.58-0.92)	0.008

[a] 144/163 patients in final analysis.
[b] Adjusted also for gender.

ULT and provide additional care to support adherence in those at risk of non-adherence.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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References

1. Dalbeth N, Gosling AL, Gaffo A, Abhishek A. Gout. Lancet 2021; 397:1843–55.
2. Richette P, Doherty M, Pascual E *et al.* 2016 updated EULAR evidence-based recommendations for the management of gout. Ann Rheum Dis 2017;76:29–42.
3. Hui M, Carr A, Cameron S *et al.*; British Society for Rheumatology Standards, Audit and Guidelines Working Group. The British Society for Rheumatology Guideline for the Management of Gout. Rheumatology (Oxford) 2017;56:1056–9.
4. Abhishek A, Doherty M. Education and non-pharmacological approaches for gout. Rheumatology (Oxford) 2018;57:i51–8.
5. Yin R, Li L, Zhang G *et al.* Rate of adherence to urate-lowering therapy among patients with gout: a systematic review and meta-analysis. BMJ Open 2018;8:e017542.
6. Russell MD, Rutherford AI, Ellis B *et al.* Management of gout following 2016/2017 European (EULAR) and British (BSR) guidelines: an interrupted time-series analysis in the United Kingdom. Lancet Reg Health Eur 2022;18:100416.
7. Dehlin M, Drivelegka P, Sigurdardottir V, Svärd A, Jacobsson LTH. Incidence and prevalence of gout in Western Sweden. Arthritis Res Ther 2016;18:164.
8. Kuo CF, Grainge MJ, Mallen C, Zhang W, Doherty M. Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study. Ann Rheum Dis 2015;74:661–7.
9. Kuo CF, Grainge MJ, Mallen C, Zhang W, Doherty M. Eligibility for and prescription of urate-lowering treatment in patients with incident gout in England. Jama 2014;312:2684–6.
10. Ho GH, Pillinger MH, Toprover M. Adherence to gout guidelines: where do we stand? Curr Opin Rheumatol 2021;33:128–34.
11. Perez-Ruiz F, Perez-Herrero N, Richette P, Stack AG. High rate of adherence to urate-lowering treatment in patients with gout: who's to blame? Rheumatol Ther 2020;7:1011–9.
12. Abhishek A, Jenkins W, La-Crette J, Fernandes G, Doherty M. 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. Rheumatology (Oxford) 2017;56:529–33.
13. Vrijens B, De Geest S, Hughes DA, ABC Project Team. A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol 2012;73:691–705.
14. Horne R, Weinman J. Self-regulation and Self-management in Asthma: exploring The Role of Illness Perceptions and Treatment Beliefs in Explaining Non-adherence to Preventer Medication. Psychology & Health 2002;17:17–32.
15. Tan C, Teng GG, Chong KJ *et al.* Utility of the morisky medication adherence scale in gout: a prospective study. Patient Prefer Adherence 2016;10:2449–57.
16. Weinman J, Graham S, Canfield M *et al.* The Intentional Non-Adherence Scale (INAS): initial development and validation. Journal of psychosomatic research 2018;115:110–6.
17. Uhlig T, Karoliussen LF, Sexton J *et al.* 12-month results from the real-life observational treat-to-target and tight-control therapy NOR-Gout study: achievements of the urate target levels and predictors of obtaining this target. RMD Open 2021;7:e001628.
18. Neogi T, Jansen TLTA, Dalbeth N *et al.* 2015 Gout classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2015;74:1789–98.
19. Chan AHY, Horne R, Hankins M, Chisari C. The Medication Adherence Report Scale: a measurement tool for eliciting patients' reports of nonadherence. Br J Clin Pharmacol 2020;86:1281–8.
20. Jónsdóttir H, Opjordsmoen S, Birkenaes AB *et al.* Medication adherence in outpatients with severe mental disorders: relation between self-reports and serum level. J Clin Psychopharmacol 2010; 30:169–75.
21. Sangha O, Stucki G, Liang MH, Fossel AH, Katz JN. The Self-Administered Comorbidity Questionnaire: a new method to assess comorbidity for clinical and health services research. Arthritis Rheum 2003;49:156–63.
22. Singh JA, Taylor WJ, Simon LS *et al.* Patient-reported outcomes in chronic gout: a report from OMERACT 10. J Rheumatol 2011; 38:1452–7.
23. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137–45.
24. Ware JE, Jr., Gandek B, Group TIP. The SF-36 Health Survey: development and use in mental health research and the IQOLA project. Int J Ment Health 1995;23:49–73.
25. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics 1993;4:353–65.
26. Hammer HB, Karoliussen L, Terslev L *et al.* Ultrasound shows rapid reduction of crystal depositions during a treat-to-target approach in gout patients: 12-month results from the NOR-Gout study. Ann Rheum Dis 2020;79:1500–5.
27. Uhlig T, Eskild T, Karoliussen LF *et al.* Two-year reduction of dual-energy CT urate depositions during a treat-to-target strategy in gout in the NOR-Gout longitudinal study. Rheumatology (Oxford) 2022;61:SI81–SI85.
28. Schulz M, Coleshill MJ, Day RO *et al.* Estimation of adherence to urate-lowering therapy in people living with gout using Australia's

Pharmaceutical Benefits Scheme and patient-reported dosing. Br J Clin Pharmacol 2024;90:1322–32.
29. Lee S, So MW, Ahn E. Long-term adherence and persistence with febuxostat among male patients with gout in a routine clinical setting. Mod Rheumatol 2019;29:662–8.
30. Coleman GB, Dalbeth N, Frampton C *et al.* Long-term follow-up of a randomized controlled trial of allopurinol dose escalation to achieve target serum urate in people with gout. J Rheumatol 2022; 49:1372–8.
31. Stephenson BJ, Rowe BH, Haynes RB, Macharia WM, Leon G; The Rational Clinical Examination. Is this patient taking the treatment as prescribed? JAMA 1993;269:2779–81.
32. Salt E, Hall L, Peden AR, Home R. Psychometric properties of three medication adherence scales in patients with rheumatoid arthritis. J Nurs Meas 2012;20:59–72.
33. De Cuyper E, De Gucht V, Maes S, Van Camp Y, De Clerck LS. Determinants of methotrexate adherence in rheumatoid arthritis patients. Clin Rheumatol 2016;35:1335–9.
34. Ceranic J, Kisic Tepavcevic D, Petronijevic M *et al.* Assessment and prediction of adherence to methotrexate using three self-report questionnaires in patients with rheumatoid arthritis. Medicina 2023;59:1446.
35. Stone JK, Shafer LA, Graff LA *et al.* Utility of the MARS-5 in Assessing Medication Adherence in IBD. Inflammatory bowel diseases 2021;27:317–24.
36. Te Paske R, Vervloet M, Linn AJ *et al.* The impact of trust in healthcare and medication, and beliefs about medication on medication adherence in a Dutch medication-using population. Journal of psychosomatic research 2023;174:111472.
37. Al Bawab AQ, Al-Qerem W, Abusara O *et al.* What are the factors associated with nonadherence to medications in patients with chronic diseases? Healthcare (Basel) 2021;9.
38. Vluggen S, Hoving C, Schaper NC, De Vries H. Psychological predictors of adherence to oral hypoglycaemic agents: an application of the ProMAS questionnaire. Psychol Health 2020;35:387–404.
39. Garcia-Marcos PW, Brand PL, Kaptein AA, Klok T. Is the MARS questionnaire a reliable measure of medication adherence in childhood asthma? J Asthma 2016;53:1085–9.
40. Sjölander M, Eriksson M, Glader EL. The association between patients' beliefs about medicines and adherence to drug treatment after stroke: a cross-sectional questionnaire survey. BMJ Open 2013;3:e003551.
41. Hu S, Terkeltaub R, Sun M *et al.* Palpable tophi and more comorbidities associated with adherence to urate-lowering medical therapy in a Chinese gout cohort. Joint Bone Spine 2022;89:105435.
42. Chung MK, Kim SS, Cheon YH *et al.*; Korean Society of Gout Research. Patient Perspectives and Preferences Regarding Gout and Gout Management: Impact on Adherence. J Korean Med Sci 2021;36:e208.
43. Singh JA, Richman J, Yang S, Bridges SL, Saag K. Allopurinol adherence and its predictors in gout: a national cohort study in US veterans. Lancet Rheumatol 2020;2:e281–e91.
44. Perez-Ruiz F, Desideri G. Improving adherence to gout therapy: an expert review. Ther Clin Risk Manag 2018;14:793–802.
45. Richardson JC, Liddle J, Mallen CD *et al.* A joint effort over a period of time: factors affecting use of urate-lowering therapy for long-term treatment of gout. BMC Musculoskelet Disord 2016;17:249.
46. Gaffo AL, Dalbeth N, Saag KG *et al.* Brief Report: validation of a Definition of Flare in Patients With Established Gout. Arthritis Rheumatol 2018;70:462–7.
47. Emad Y, Dalbeth N, Weinman J, Chalder T, Petrie KJ. Can smartphone notifications help with gout management? A feasibility study. J Rheumatol 2024;51:189–96.

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