RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

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

Till Uhlig ,[1,2] Lars F Karoliussen,[1] Joseph Sexton,[1] Tove Borgen,[1] Espen A Haavardsholm,[1,2] Tore K Kvien ,[1] Hilde Berner Hammer [1,2]

To cite: 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. doi:10.1136/rmdopen-2021-001628

Some of the results from this study have been presented in a poster at EULAR 2019, and EULAR 2020 and at ACR 2019 ACR/ARP Annual Meeting.

Received 12 February 2021
Revised 1 March 2021
Accepted 5 March 2021

[1]Rheumatology, Diakonhjemmet Hospital, Oslo, Norway
[2]Institute of Clinical Medicine, University of Oslo, Oslo, Norway

Correspondence to
Dr Till Uhlig;
tillmann.uhlig@medisin.uio.no

ABSTRACT

Objectives Gout is often not adequately treated, and we aimed to apply urate lowering treatment (ULT) combined with individual information to achieve target serum urate (sUA) in clinical practice, and to identify predictors of achievement of this sUA target.

Methods Patients with a recent gout flare and sUA >360 µmol/L (>6 mg/dL) were consecutively included in a single-centre study and managed with a treat-to-target approach combining nurse-led information about gout with ULT. All patients were assessed with tight controls at baseline, 1, 2, 3, 6, 9 and 12 months including clinical examination, information on demographics, lifestyle, self-efficacy and beliefs about medicines. The treatment target was sUA <360 µmol/L and multivariable logistic regression was used to identify predictors of target attainment with ORs and 95% CIs.

Results Of 211 patients (mean age 56.4 years, disease duration 7.8 years, 95% males), 186 completed the 12-month study. Mean sUA levels decreased from baseline mean 500 to 311 µmol/L at 12 months with 85.5% achieving the treatment target. Alcohol consumption at least weekly versus less frequently (OR 0.14; 95% CI 0.04 to 0.55) as well as beliefs in overuse of medicines (OR per unit 0.77; 95 CI 0.62 to 0.94) decreased the chance of reaching the treatment target, while higher self-efficacy for arthritis symptoms (OR 1.49 per 10 units; 95% CI 1.09 to 2.05) increased the likelihood.

Conclusions This study shows that target sUA can be achieved with ULT in most patients. Less self-reported alcohol consumption, low beliefs in overuse of medicines and higher self-efficacy are associated with treatment success.

Key messages

What is already known about this subject?

- In patients with gout, urate lowering treatment (ULT) leads to achieving a low level of serum urate (sUA).

What does this study add?

- This large longitudinal study of patients with gout with a treat-to-target approach of urate lowering therapy in combination with information by a study nurse and frequent follow-up resulted in satisfactory sUA levels in about 85% of patients after 12 months.
- More frequent alcohol consumption and general beliefs on that drugs are overused decreased the change achieving low sUA target values, whereas self-efficacy contributed to a good treatment outcome.

How might this impact on clinical practice?

- Successful gout management is attainable, and more attention towards addressing modifiable factors could further increase long-term adherence to ULT and health promoting lifestyle.

INTRODUCTION

Gout is a prevalent inflammatory joint disease.[1–3] Long-standing hyperuricaemia leads to formation and deposition of monosodium urate crystals in joints and other tissues with inflammation causing erosions, severe pain and disability.[4–6] Globally, gout entails a significant burden of disease.[7]

To reduce disease burden, initiation of urate lowering therapy (ULT) is recommended, and should be considered shortly after diagnosis.[8] However, despite established and clear treatment recommendations[8–10] and easily available and effective medication, gout is often poorly managed,[11] and ULT is seldom started early in the disease.[12] The concept of ULT gout treatment is challenged[13] and not well perceived by physicians.[14]

Physicians do not view the impact of gout nearly as severely as patients do,[15] and the majority of patients do not reach required target levels.[16] These practices have led to

poor medication adherence,[17] with as few as 10% of patients with gout adhering to their treatment.[18]

A nurse-led study from Nottingham, UK, involved patients and included lifestyle advice along with a treat-to-target strategy for ULT, demonstrating that >90% of participants reduced their serum urate (sUA) to <360 µmol/L at 1 year.[19] A subsequent new randomised controlled trial demonstrated similar effectiveness over 2 years as compared with usual general practitioner-led care.[20]

Reasons for unsuccessful treatment of gout with ULT may be inherent to treatment traditions among physicians[21] contributing to low adherence to coping, lifestyle changes and medication. High alcohol consumption is seen in many patients with gout,[6] but psychological factors, such as self-efficacy and beliefs in medicines have not been studied. Further, there is a scarcity of prospective clinical practice research to examine the effectiveness of ULT in a tight control and treat-to-target strategy and to identify factors associated with the sUA outcome (the target). In this study, we applied ULT and patient information in tightly scheduled follow-up visits to estimate how often the sUA target could be reached, and examined which factors predicted achievement of the target.

METHODS

Study design and participants

NOR-Gout (Gout in Norway) is a prospective, observational single-centre study in a hospital-based rheumatology unit. Patients were eligible if having a gout flare within the last month, had increased sUA levels (>360 µmol/L), and no contraindication for ULT. No other previous gout flares were required. They were consecutively included according to the protocol (ACTRN12618001372279). All had been diagnosed with gout based on identification of monosodium urate crystals in polarised microscopy after arthrocentesis and also satisfied the American College of Rheumatology/EULAR classification criteria.[22] Exclusion criteria were unstable medical conditions (eg, ischaemic heart disease, impaired liver function); known stage 3b or higher chronic kidney disease (estimated glomerular filtration (eGFR) rate/creatinine clearance <45 mL/min); recent surgery or gastrointestinal bleed; and age <18 years. Study candidates were identified during an acute clinical gout flare after examination in the department. Persons indicating willingness to participate in the study were contacted by a study nurse from the outpatient clinic for prescreening, received written information, and were scheduled for a baseline rheumatology outpatient visit at Diakonhjemmet Hospital. The sponsor of the study was Diakonhjemmet Hospital.

Treatment strategy

Trained research nurses had at the baseline visit individual consultations with patients comprising:

a. Information on disease and disease process, diagnosis, causes, recommended treatments, disease control.
b. Lifestyle advocation on exercise, weight reduction and alcohol consumption.
c. Discussion of patient expectations, advice when to get help and coping. Further, a brochure addressed advice on diet.

At every visit, drug use was recorded for non-steroidal anti-inflammatory drugs (NSAID), colchicine, prednisolone and for ULT (allopurinol, febuxostat), registering drug dosage, adverse events and symptoms of flares.

All patients not already on ULT started as recommended[8] oral allopurinol 100 mg one time a day and escalated in 100 mg increments monthly according to sUA concentrations to a maximum of 900 mg daily. If intolerance for allopurinol, febuxostat was started at 40 mg one time a day and escalated monthly to 80 and 120 mg as needed. Probenecid or lesinurad could be added if necessary, but were not used in any patients. Patients received flare prophylaxis with colchicine 0.5–1 mg daily for 3–6 months. In this treat-to-target approach, ULT was escalated to reach <360 µmol/L (or <300 µmol/L if clinical tophi were present) and the dose was maintained when the target was reached.

Visits

All patients were assessed both by a study nurse and a rheumatologist (HBH, LK) at baseline as well as after 3, 6 and 12 months. Additional fixed visits with only study nurse were at 1, 2 and 9 months, and if necessary monthly, until the treatment target was reached. Telephone contact with review of the sUA results could substitute the face-to-face visits.

Covariates

Demographics and self-reported measures

At baseline, patients reported age, gender, ethnicity, marital status, family history for gout, disease duration, highest level of education, comorbidities and working status. For comorbidities, the Self-Administered Comorbidity Questionnaire was used (range 0–36)[23]; it includes 12 medical problems, allocating 1 point per problem including presence, receiving treatment and causing a functional limitation.

Alcohol consumption was assessed with the categories 'Daily', 'Weekly', 'Monthly' and 'Never', then aggregating the categories to daily/weekly and monthly/never. Daily and previous smoking, consumption of daily glasses with sugar sweetened drinks, and the frequency of physical activity were reported by patients.

At baseline, information on number of flares ever and during the last year (before the recent flare) was collected as well as pain severity during the most recent and the strongest flare (0–10 numerical rating scales), with 0=no pain and 10=unbearable pain.

Questionnaires at visits recorded present joint pain due to gout, general pain, fatigue and patient global assessment of disease activity on 0–10 numerical rating scales.

Physical function was measured with the Health Assessment Questionnaire (HAQ) without adjustment for help or devices.[24] Health status was assessed by the Short Form general health questionnaire.[25]

Self-efficacy with subscales for pain (five items) and symptoms (six items) was measured with the Arthritis Self-Efficacy Scales.[26] This instrument measures whether patients have confidence in coping with pain, function and other symptoms due to arthritis (numeric rating scales 10–100, 100=highest).

The Beliefs about Medicines Questionnaire (BMQ)[27] explores patients' beliefs about medicines and includes scales on perceived necessity or concerns for the patient's own medicines (5 items each, range 5–25), and for perceived general overuse and harm of medicines (4 items each with range 4–16). Items were scored on Likert scale 1–5, 5=highest agreement, and a high scale score reflects stronger belief in the expressed concept.

Clinical assessments

Clinical assessments included weight and height for calculation of body mass index (BMI) and 44-swollen and tender joint counts. Clinical subcutaneous tophi were counted. The largest was defined as index tophus, measured in length and width in millimetres.

Laboratory assessments

Laboratory examinations included sUA (µmol/L), erythrocyte sedimentation rate mm/hour, C reactive protein mg/L, creatinine (µmol/L), eGFR (mL/min/1.73 m^2), as well as hematological status at baseline and each follow-up visit.

Outcomes

The primary outcome in this study was the percentage of patients who achieved sUA concentrations<360 µmol/L at 12 months, also for patients with tophi where a more ambitious target <300 µmol/L was applied. Secondary outcomes in the study were baseline factors tested for prediction of the primary outcome at 12 months.

Statistics

Descriptive measures of baseline variables are presented using absolute and relative frequency, mean and SD. Differences between groups were explored by use of independent samples t-test and by the χ^2 test or Fisher's exact. OR and their 95% CIs were calculated by logistic regression analyses. Bivariate analyses were performed first. Candidate predictor variables of sUA target attainment were selected from the baseline data, based on their potential clinical relevance. We then included these in multivariable logistic regression analyses adjusting for age, gender, race, education, disease duration, BMI, comorbidities and baseline sUA. In the full model, we also included from bivariate analyses candidate variable if p<0.10 and we stepwise removed other variables not statistically significant. The patients not completing the 12-month assessment followed the same demographic profile as the completers. P<0.05 was defined as statistically significant. We did not adjust for multiple analyses. Calculations were performed with IBM SPSS statistics (V.25).

RESULTS

Patient characteristiscs

Among patients with a recent gout flare, 242 patients were identified and prescreened for inclusion into the study, and 211 met inclusion criteria. Reason for non-inclusion were not meeting the required sUA or eGFR values (n=12), unpractical schedule (n=11), withdrawal of consent (n=7) and failure to meet for the scheduled baseline visit (n=1).

Of 211 patients, 186 (88.2%) completed the visit for the primary sUA endpoint at 12 months. The number of patients meeting for other time points was 202 (month 1), 193 (month 2), 189 (month 3), 176 (month 4), 75 (month 5), 187 (month 6), 55 (month 7), 42 (month 8), 167 (month 9), 60 (month 10), 27 (month 11). Patients not completing the 12-month follow-up had shorter disease duration, were more frequently daily smokers (both p<0.01), less frequently educated at college/university, married/cohabiting, working, physically active and had fewer previous gout flares (all p<0.05).

Patient baseline characteristics are provided in table 1. Females constituted 4.7% of included patients, and in the total cohort 16.6% had a clinical tophus.

Primary outcome

From baseline to 12 months, mean (SD) sUA decreased in all patients from 500 (77) to 311 (48) µmol/L (p<0.001), and in patients not reaching the target from 517 (117) to 393 (33) µmol/L (p<0.001, data not shown).

Table 2 gives sUA levels and frequencies for achieving sUA <360 µmol/L during the 12-month period, and separately also for the subgroup of patients with tophi for achieving sUA <300 µmol/L. A total of 85.5% of all patients at the 12-month visit reached the target sUA <360 µmol/L, and 69.3% already after 3 months. The proportions reaching the target did not increase between months 6 and 12. For the subgroup of patients with clinical subcutaneous tophi (n=35), sUA continuously declined and 54.8% met the treatment target <300 µmol/L after 12 months (table 2).

Medication and secondary outcomes

All 211 patients initiated or escalated ULT. Only 14.7% of patients had ever used allopurinol and none had used febuxostat, while 78% had experience with NSAID, and about half with colchicine and prednisolone. During the course of the first year, prescription of allopurinol decreased from 95.0% to 87.6%, and increased from 3.5% to 12.4% for febuxostat (table 3). Mean doses for allopurinol remained just below 300 mg and below 60 mg for febuxostat.

A flare during the study was experienced by 80.6% (150/187). During the 12-month study period, the percentage of patients with at least one swollen joint

Table 1 Baseline characteristics of all patients

	N	% or mean (SD)
Age (years)	211	56.4 (13.7)
Male	201/211	95.3%
Caucasian	183/202	90.6%
Disease duration (years)	204	7.8 (7.6)
College education	118/206	57.3%
Married/cohabiting	155/208	74.5%
Working	133/208	63.9%
Body mass index (kg/m^2)	211	28.8 (4.5)
Comorbidities (SCQ sum)	210	3.7 (3.2)
Physical activity ≥3 times weekly	163/207	30.4%
Smoking, daily	23/208	11.1%
Alcohol consumption	207	
Daily	17	8.2%
Weekly	111	53.6%
Monthly	55	26.6%
Never	24	11.6%
Sugar sweetened drinks consumed daily	80/207	38.6%
Tophus present (≥1)	35/211	16.6%
No. tophi	211	
0	176	83.4%
1–5	30	14.2%
>5	5	2.4%
Allopurinol use ever	31/211	14.7%
NSAID use ever	160/205	78.0%
Colchicine use ever	107/201	53.2%
Prednisolone use ever	91/199	45.7%
Baseline sUA (µmol/L)	211	500 (77)
ESR (mm/hour)	199	14.5 (14.2)
Creatinine (µmol/L)	211	96.3 (18.6)
eGFR (mL/min per 1.73 m^2)	210	78 (19)
No. flares before recent one	208	
None	16	7.7%
1	25	12.0%
2–5	65	31.3%
>5	102	49.0%
Other flare experienced last 12 months before inclusion?	151/206	73.4%
Strongest joint pain ever (0–10)	208	8.4 (1.6)
Joint pain last flare (0–10)	207	7.5 (5.5)
Swollen joint present	72/209	34.4%
Tender joint present	110/210	52.4%
Health Assessment Questionnaire (0–3)	209	0.38 (0.57)
SF-36 physical component summary (0–100)	204	39.1 (11.1)
SF-36 mental component summary (0–100)	204	50.0 (10.2)
Self-efficacy pain (10–100)	209	65.3 (19.5)
Self-efficacy symptoms (10–100)	205	72.6 (15.1)
Beliefs about Medicines Questionnaire		
Necessity subscale (5–25)	198	17.9 (4.4)
Concerns subscale (5–25)	197	13.4 (4.9)
Overuse subscale (4–16)	203	10.6 (2.8)
Harm subscale (4–16)	203	9.4 (2.4)

eGFR, electronic glomerular filtration rate; ESR, erythrocyte sedimentation rate; NSAID, non-steroidal anti-inflammatory drug; SCQ, Self-Administered Comorbidity Questionnaire; SF-36, Short-Form 36.

was reduced from 35.3% (65/184) to 10.8% (20/185) (p<0.001) and with tophi from 16.7% (31/186) to 11.3% (21/186) (p=0.01), and with no statistically significant differences with respect to whether the sUA target was achieved or not. Creatinine and eGFR values remained unchanged, 96 (17) to 98 (19) µmol/L and 78.0 (19) to 79 (19) mL/min/1.73 m^2, respectively.

Bivariate analyses examined factors leading to achieving the treatment target <360 µmol/L after 12 months (table 4). Patients achieving the treatment target had less belief that medicines were generally overused compared with those not achieving the target (p=0.04).

Variables as predictors for reaching the treatment target

Baseline variables which could predict achieving the treatment target of sUA <360 µmol/L were then analysed in bivariate and multivariable logistic regression analyses and are described in table 5. In the first model, crude baseline values are shown with OR and CIs. Then, adjustments were made for age, gender, ethnicity, education, disease duration, BMI, comorbidities and baseline sUA. The final model is also fully adjusted for these variables.

Some factors predicted achieving the sUA target after 12 months in partly adjusted analyses: alcohol consumption at least weekly/daily versus monthly/never, low physical function according to HAQ, self-efficacy for symptoms and a perception of general overuse of medicines (BMQ). In the fully adjusted logistic regression model, three factors statistically significantly predicted

Table 2 Serum urate levels and frequency of target achievement (sUA <360 µmol/L) in patients assessed during time points. In addition, informationfor the subgroup with clinically detectable tophi with sUA target sUA<300µmol/L

Month	0	1	2	3	6	9	12
All patients							
sUA µmol/L (mean, SD)	500 (78)	413 (77)	371 (64)	341 (61)	327 (59)	316 (56)	311 (48)
Target <360 achieved (%) N	0 0/211	21.3 43/202	48.7 94/193	69.3 131/189	80.7 151/187	81.9 136/166	85.5 159/186
Patients with tophi							
sUA µmol/L (mean, SD)	506 (80)	431 (78)	388 (70)	334 (56)	318 (59)	317 (59)	298 (52)
Target <300 achieved (%) N	0 0/35	2.9 1/35	12.1 4/33	25.0 8/32	38.7 12/31	46.2 12/26	54.8 17/31

achieving the treatment target after 12 months (table 5); higher alcohol consumption at least weekly and belief that medicines were overused reduced the odds for achieving this target, whereas higher self-efficacy for symptoms, as an indicator for coping, increased it.

Neither baseline sUA nor final ULT dose with allopurinol were associated with the treatment target. Also, previous flares, baseline tophi, presence of swollen joints, as well as flares during the study were unrelated to reaching the treatment target. Sensitivity analyses examined also factors which predicted achievement of the most stringent treatment target of sUA <300 µmol/L in 35 patients with tophi. In bivariate analyses, only two variables—daily working and eGFR—were statistically significantly related to this target, but in multivariate analyses none of these or any other variables predicted reaching the target.

DISCUSSION

In this study, we examined how many patients with gout reached the sUA target of <360 µmol/L) after 1 year when they were followed frequently by a nurse and a rheumatologist with information and escalating ULT as needed. This target was reached by 85.5% of patients completing the 12-month follow-up, in almost 70% already after 3 months, and few other patients achieved the treatment target after 6 months. We further identified predictors of reaching the treatment target. More frequent alcohol consumption at least weekly as well as a belief that drugs are overused reduced odds for achieving the target, while coping with arthritis symptoms increased the odds. Identification of all these three factors as predictors for achieving the treatment target are novel findings. Our study is large and with frequent follow-up visits, showing that the promoted urate target is realistic in daily clinical practice if patients are followed by a treat-to-target strategy.

The response rate in a randomised controlled trial from Nottingham, UK, was even higher than in our study with 95% after both 1 and 2 years, when care was provided by a nurse combining ULT and education as compared with primary care.[20] A recent study from the Netherlands compared two treatment strategies,[28] a more ambitious approach with a target of sUA <300 mol/L as compared with a target <360 µmol/L. During follow-up, an sUA value of <360µml/L was numerically more frequently reached in the more ambitious approach by 83% versus 74%, but differences were not statistically significant.[28] In a Mexican study, the target sUA was achieved in only 50%–70% after 3–4 years in spite of regular visits,[29] and response rates by 12 months among general practitioners in the UK with sUA <360 µmol/L were 45%.[30]

Table 3 Prescription of allopurinol and febuxostat during follow-up

	% (n) allopurinol	% (n) febuxostat	Mean mg dose (range) allopurinol users	Mean mg dose (range) febuxostat users	Total prescription urate lowering therapy at follow-up
Before Baseline	14.7 (31/211)	0	109 (100–500)		14.7%
Month 1	95.0 (192/202)	3.5 (7/202)	119 (100–600)	51 (40–80)	98.5%
Month 2	95.3 (184/193)	4.7 (9/193)	190 (50–700)	49 (40–80)	100.0%
Month 3	94.2 (178/189)	5.8 (11/189)	236 (50–700)	54 (40–80)	100.0%
Month 6	90.4 (169/187)	8.6 (16/187)	273 (100–800)	52 (40–120)	99.0%
Month 9	89.2 (149/167)	9.6 (16/167)	280 (100–900)	50 (40–80)	95.8%
Month 12	87.6 (163/186)	12.4 (23/186)	289 (100–900)	59 (40–120)	100.0%

Table 4 Participant baseline variables by response status after 12 months

	N	% or mean (SD)	Target achieved (sUA <360 µmol/L) N=159	Target not achieved (sUA >360 µmol/L) N=27	P value
Age (years)	186	56.8 (13.6)	57.4 (13.5)	53.5 (13.4)	0.17
Male	186	95.2%	94.3%	100%	0.21
White	180	90.6%	91.6%	84.6%	0.26
Disease duration (years)	182	8.2 (7.)	8.0 (7.8)	9.4 (8.3)	0.42
Education level college	182	60.4%	61.5%	53.8%	0.46
Married/cohabiting	183	77.0%	77.7%	73.1%	0.60
Working versus not	183	66.7%	66.9%	65.9%	0.52
Body mass index	186	28.9 (4.6)	28.8 (4.6)	29.6 (4.5)	0.41
Comorbidities (SCQ sum)	185	3.8 (3.3)	3.9 (3.3)	3.0 (3.3)	0.18
Physical activity ≥3 times weekly	182	33.0%	33.8%	28.0%	0.57
Smoking, daily	183	8.2%	7.6%	11.5%	0.93
Alcohol consumption (at least weekly)	182	61.5%	59.0%	76.9%	0.08
Sugar sweetened drinks consumed daily	182	37.9%	38.5%	34.6%	0.71
Tophus present (≥1)	186	16.7%	18.2%	7.4%	0.16
Allopurinol ever use	186	14.0%	13.8%	14.8%	0.90
NSAID ever use	180	79.4%	77.9%	88.5%	0.22
Colchicine ever use	177	52.5%	53.0%	50.0%	0.78
Prednisolone ever use	176	49.4%	49.7%	48.0%	0.88
Baseline sUA (µmol/L)	186	498 (80)	495 (72)	517 (117)	0.36
ESR (mm/hour)	176	14 (14)	14 (14)	16 (14)	0.57
Creatinine (µmol/L)	186	96 (18)	96 (17)	98 (18)	0.55
eGFR (mL/min)	185	78 (18)	78 (18)	79 (20)	0.69
No. flares before recent one	187				0.82
0–1	34	18.6%	17.9%	23.0%	
2–5	53	29.0%	29.3%	26.0%	
>5	96	52.5%	52.9%	50.0%	
Other flare last 12 months before inclusion	181	75.1%	74.2%	80.8%	0.79
Strongest joint pain ever (0–10)	183	8.3 (1.6)	8.4 (1.5)	8.1 (2.0)	0.48
Joint pain last flare (0–10)	182	7.1 (2.0)	7.1 (1.9)	7.4 (2.4)	0.40
Swollen joint present	184	35.3%	35.7%	33.3%	0.82
Tender joint present	184	53.3%	53.5%	51.9%	0.87
Health Assessment Questionnaire	184	0.36 (0.57)	0.33 (0.54)	0.56 (0.71)	0.13
SF-36 physical component summary (0–100)	182	38.9 (10.8)	39.2 (10.5)	37.1 (12.4)	0.38
SF-36 mental component summary (0–100)	182	50.4 (10.1)	50.5 (10.5)	50.2 (7.6)	0.89
Self-efficacy pain (10–100)	184	65.3 (19.2)	65.6 (19.1)	63.9 (20.1)	0.68
Self-efficacy symptoms (10–100)	180	72.8 (17.0)	73.7 (16.9)	66.9 (17.2)	0.06
Beliefs about Medicines Questionnaire					
Necessity (5–25)	176	17.0 (4.3)	17.0 (4.3)	16.7 (4.5)	0.74
Concern (5–25)	175	13.4 (4.4)	13.4 (4.5)	13.3 (3.7)	0.92
Overuse (4–16)	179	10.6 (2.8)	10.4 (2.7)	11.6 (2.7)	0.04
Harm (4–16)	179	9.4 (2.4)	9.3 (2.5)	10.0 (2.0)	0.18

eGFR, electronic glomerular filtration rate; ESR, erythrotcyte sedimentation rate; NSAID, non-steroidal anti-inflammatory drug; SCQ, Self-Administered Comorbidity Questionnaire; SF-36, Short-form 36.

Table 5 Predictors of baseline variables for reaching the treatment target serum urate (sUA) <360 µmol/L

	Unadjusted OR (95% CI)	Partly adjusted OR (95% CI)*	Fully adjusted model OR (95% CI)†	Fully adjusted model p value
Age (per 10 years)	1.23 (0.99 to 1.66)	1.06 (0.72 to 1.57)		
Disease duration (years)	0.98 (0.93 to 1.03)	0.99 (0.94 to 1.05)		
Education college	1.37 (0.60 to 3.16)	1.36 (0.54 to 3.42)		
Body mass index	0.96 (0.87 to 1.05)	0.98 (0.89 to 1.09)		
Comorbidities (SCQ sum)	1.10 (0.96 to 1.26)	1.09 (0.90 to 1.31)		
Alcohol (at least weekly vs less)	0.43 (0.16 to 1.13)	0.24 (0.04 to 0.78)	0.14 (0.04 to 0.55)	0.005
Baseline sUA (µmol/L)	0.997 (0.992 to 1.002)	0.996 (0.991 to 1.001)		
Health Assessment Questionnaire	0.56 (0.30 to 1.04)	0.47 (0.20 to 0.99)		
Self-efficacy pain subscale (10 units)	1.05 (0.85 to 1.30)	1.13 (0.88 to 1.04)		
Self-efficacy symptoms scale (10 units)	1.26 (0.99 to 1.61)	1.38 (1.04 to 1.84)	1.49 (1.09 to 2.05)	0.014
Beliefs about Medicines Questionnaire				
Necessity (5–25)	1.02 (0.91 to 1.12)	1.03 (0.91 to 1.16)		
Concern (5–25)	1.00 (0.91 to 1.11)	1.03 (0.93 to 1.14)		
Overuse (4–16)	0.84 (0.71 to 0.99)	0.83 (0.70 to 0.99)	0.77 (0.62 to 0.94)	0.013
Harm (4–16)	0.88 (0.74 to 1.06)	0.88 (0.72 to 1.07)		

*Adjusted for age, gender, race, education, disease duration, body mass index, comorbidities, and baseline sUA and all other variables in logistic regression model.
†Adjusted for age, gender, race, education, disease duration, body mass index, comorbidities and baseline sUA and all other variables remaining in model logistic regression model.
SCQ, self-administered comorbidity questionnaire.

Many patients with gout have high alcohol intake,[6 31] and alcohol intake is related to the incidence of gout[32] and frequency of flares.[33] Compared with men who did not drink alcohol, the multivariate relative risk of gout increased dose dependently. We found that patients consuming alcohol at least weekly at baseline had a clearly reduced chance (OR 0.14) to prospectively achieve the treatment target as compared with less frequent or no alcohol consumption. This extends knowledge on the unfavourable effect of alcohol consumption from the risk of gout flares[34] to achieving the sUA target.

Beliefs about medicines and patients' attitudes towards administering medications are generally a good indicator of their intentions to adhere to treatments.[35] One cross-sectional study from Hong Kong applied the BMQ in a mix of hospital outpatients including gout,[36] and showed that the majority of the participants had strong beliefs that medicines were necessary and beneficial, while a minority had strong beliefs that medicines, in general, were overused, harmful and causing them concern. Our study was the first to longitudinally apply the BMQ with four subscales in gout and found that higher belief in overuse of medication independently impeded achieving the treatment goal, whereas beliefs on necessity, concerns and harm of medication did not. In absence of other reports on the relationship of BMQ with treatment success in gout, we assume that information on dose adjustment in ULT would motivate and convince patients to take their medication and therefore improve adherence to ULT.[37] Qualitative research has also shown that trust in doctor and medication effectiveness were identified as the most important factors for adherence,[38] indicating that thorough information and personal contact with the health provider could improve medication compliance.

Self-efficacy is related to the belief that one can cope with pain, reduced function or symptoms mediated by the disease. While no study previously assessed self-efficacy[26] in gout, one study applied qualitative research and found that a sense of control was described as an important contributor to the overall patient experienced severity of gout.[39] These results were supported by a study in diabetes[40] where self-efficacy was increased by monitoring self-management patterns and accordingly providing feedback. In our study, information by the nurse as well as information about the decreasing load of crystal depositions during ultrasound assessments[41] during the tight frequency of study visits may have contributed to increased self-efficacy and improved adherence.

We found no association between baseline sUA value and meeting the sUA target. An interpretation could be that persistent treatment with frequent adjustment of ULT was continuously applied to all patients when needed, making the initial sUA level less important. Two randomised controlled trials found that baseline sUA was related to the treatment response as measured by sUA.[42 43] Further, healthcare access, patient and provider factors as well as presence of comorbidities were recently

reported associated to achieving and maintaining the target sUA level.[44]

Limitations of our study include that patients were entered from only one centre and findings cannot necessarily be extrapolated to other clinical settings. Second, the observational nature and lack of a control group in our study does not allow causal inferences. Further limitations were exclusion of patients with chronic kidney disease stage 3b and higher, and assessment of alcohol consumption by one question only.

Our findings support that existing treatment recommendations with a focus on ULT as well as information leads to achievement of the treatment target in the majority of patient.[8–10] In this large prospective follow-up study in clinical practice, we found that patient information with escalating ULT lead to meeting the treatment target in gout in the vast majority of patients (about 85%) at follow-up. This study also provided new knowledge on predictors for the treatment outcome in gout. More frequent alcohol consumption and general beliefs that drugs are overused decreased the change achieving low sUA target values, whereas self-efficacy contributed to a good treatment outcome.

Successful gout management is attainable, and more attention towards addressing these modifiable factors could increase long-term adherence to ULT and health promoting lifestyle. Further research is required to investigate modifiable factors for achieving successful gout outcomes such as target sUA.

Acknowledgements The authors thank research secretary Mona Thorkildsen for organisation and research nurses Gina Stenberg, Anita Reinhard, Heidi Lunøe and Ingerid Müller who contributed as trained study nurses in the follow-up of the treat-to-target approach, and patient representatives Espen Reksten and Jan Petter Synnestvedt for good advice.

Contributors TU has made a substantial contributions to the conception and design of the work; the acquisition of data, some of the analysis, interpretation of data for the work; and drafted the manuscript as well as revising it critically for important intellectual content; and given a final approval of the version to be published; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. LFK, TB, EAH, TKK, and HBH has given substantial contributions to the design of the study as well as the interpretation of data for the work; and revised the manuscript critically for important intellectual content; and given a final approval of the version to be published; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. JS has given substantial contributions to the design of the study as well as the interpretation of data for the work as a statistician; and revised the manuscript critically for important intellectual content; and given a final approval of the version to be published; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding There was no external funding, and the study was performed by employees at National Advisory Unit on Rehabilitation in Rheumatology (NKRR) and Division of Rheumatology and Research, Diakonhjemmet Hospital, Oslo, Norway.

Competing interests TU reports personal fees from Grünenthal and Novartis, outside the submitted work. EAH reports personal fees from Pfizer, UCB, Eli Lilly, Celgene, Janssen-Cilag, AbbVie and Gilead outside the submitted work. TKK reports grants and personal fees from AbbVie, MSD, UCB, Hospira/Pfizer, Eli-Lilly, grants from BMS, personal fees from Roche, Hikma, Orion, Sanofi, Celltrion, Sandoz, Biogen, Amgen, Egis, Ewopharma and Mylan, outside the submitted work. HBH reports personal fees from AbbVie, Lilly and Novartis, outside the submitted work.

Patient and public involvement statement A patient research partner with gout participated in the project and took part in the discussion of the research questions and outcome measures. Further, the patient research partner evaluated the burden of study participation and supported how patients were recruited.

Patient consent for publication Not required.

Ethics approval The study was approved by the Norwegian Regional Committee for Medical and Health Research Ethics South East (reference number 2015/990) and the patients gave their written informed consent according to the Declaration of Helsinki.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The data will be shared if there is a reasonable request for it.

ORCID iDs
Till Uhlig http://orcid.org/0000-0002-6881-9552
Tore K Kvien http://orcid.org/0000-0002-8441-3093
Hilde Berner Hammer http://orcid.org/0000-0001-7317-8991

REFERENCES

1 Kuo C-F, Grainge MJ, Mallen C, *et al*. Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study. *Ann Rheum Dis* 2015;74:661–7.
2 Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National health and nutrition examination survey 2007-2008. *Arthritis Rheum* 2011;63:3136–41.
3 Dehlin M, Drivelegka P, Sigurdardottir V, *et al*. Incidence and prevalence of gout in Western Sweden. *Arthritis Res Ther* 2016;18:164.
4 Khanna PP, Nuki G, Bardin T, *et al*. Tophi and frequent gout flares are associated with impairments to quality of life, productivity, and increased healthcare resource use: results from a cross-sectional survey. *Health Qual Life Outcomes* 2012;10:117.
5 Chandratre P, Roddy E, Clarson L, *et al*. Health-Related quality of life in gout: a systematic review. *Rheumatology* 2013;52:2031–40.
6 Scirè CA, Manara M, Cimmino MA, *et al*. Gout impacts on function and health-related quality of life beyond associated risk factors and medical conditions: results from the King observational study of the Italian Society for rheumatology (Sir). *Arthritis Res Ther* 2013;15:R101.
7 Kiadaliri AA, Uhlig T, Englund M. Burden of gout in the Nordic region, 1990-2015: findings from the global burden of disease study 2015. *Scand J Rheumatol* 2018;47:410–7.
8 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.
9 Kiltz U, Smolen J, Bardin T, *et al*. Treat-to-target (T2T) recommendations for gout. *Ann Rheum Dis* 2017;76:632–8.
10 FitzGerald JD, Dalbeth N, Mikuls T, *et al*. 2020 American College of rheumatology guideline for the management of gout. *Arthritis Rheumatol* 2020;72:879–95.
11 Doherty M, Jansen TL, Nuki G, *et al*. Gout: why is this curable disease so seldom cured? *Ann Rheum Dis* 2012;71:1765–70.
12 Kuo C-F, Grainge MJ, Mallen C, *et al*. Eligibility for and prescription of urate-lowering treatment in patients with incident gout in England. *JAMA* 2014;312:2684–6.
13 Qaseem A, Harris RP, Forciea MA, *et al*. Management of acute and recurrent gout: a clinical practice guideline from the American College of physicians. *Ann Intern Med* 2017;166:58–68.
14 Abhishek A, Doherty M. Education and non-pharmacological approaches for gout. *Rheumatology* 2018;57:i51–8.
15 Lee SJ, Hirsch JD, Terkeltaub R, *et al*. Perceptions of disease and health-related quality of life among patients with gout. *Rheumatology* 2009;48:582–6.
16 Juraschek SP, Kovell LC, Miller ER, *et al*. Gout, urate-lowering therapy, and uric acid levels among adults in the United States. *Arthritis Care Res* 2015;67:588–92.
17 Scheepers LEJM, van Onna M, Stehouwer CDA, *et al*. Medication adherence among patients with gout: a systematic review and meta-analysis. *Semin Arthritis Rheum* 2018;47:689–702.

18 Roddy E, Zhang W, Doherty M. Concordance of the management of chronic gout in a UK primary-care population with the EULAR gout recommendations. *Ann Rheum Dis* 2007;66:1311–5.
19 Rees F, Jenkins W, Doherty M. Patients with gout adhere to curative treatment if informed appropriately: proof-of-concept observational study. *Ann Rheum Dis* 2013;72:826–30.
20 Doherty M, Jenkins W, Richardson H, *et al*. Efficacy and cost-effectiveness of nurse-led care involving education and engagement of patients and a treat-to-target urate-lowering strategy versus usual care for gout: a randomised controlled trial. *Lancet* 2018;392:1403–12.
21 Lioté F, Choi H. Managing gout needs more than drugs: 'Il faut le savoir-faire, l'Art et la maniere'. *Ann Rheum Dis* 2013;72:791–3.
22 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.
23 Sangha O, Stucki G, Liang MH, *et al*. The self-administered comorbidity questionnaire: a new method to assess comorbidity for clinical and health services research. *Arthritis & Rheumatism* 2003;49:156–63.
24 Fries JF, Spitz P, Kraines RG, *et al*. Measurement of patient outcome in arthritis. *Arthritis & Rheumatism* 1980;23:137–45.
25 Ware, Jr. JE, Gandek BWare JE, Jr.,. The SF-36 health survey: development and use in mental health research and the IQOLA project. *Int J Ment Health* 1994;23:49–73.
26 Lorig K, Chastain RL, Ung E, *et al*. Development and evaluation of a scale to measure perceived self-efficacy in people with arthritis. *Arthritis Care Res.* 1989;32:37–44.
27 Horne R, Weinman J. Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. *J Psychosom Res* 1999;47:555–67.
28 Kampe R, Durme C, Janssen M, *et al*. Comparative study of Real-Life management strategies in gout: data from two Protocolized gout clinics. *Arthritis Care Res* 2020;72:1169–76.
29 Alvarado-de la Barrera C, López-López CO, Álvarez-Hernández E, *et al*. Are target urate and remission possible in severe gout? A five-year cohort study. *J Rheumatol* 2020;47:132–9.
30 Roddy E, Packham J, Obrenovic K, *et al*. Management of gout by UK rheumatologists: a British Society for rheumatology national audit. *Rheumatology* 2018;57:826–30.
31 Te Kampe R, Janssen M, van Durme C. Sex differences in the clinical profile among patients with gout: cross-sectional analyses of an observational study. *The Journal of Rheumatology* 2021;48:286–92.
32 Choi HK, Atkinson K, Karlson EW, *et al*. Alcohol intake and risk of incident gout in men: a prospective study. *The Lancet* 2004;363:1277–81.
33 Neogi T, Chen C, Niu J, *et al*. Alcohol quantity and type on risk of recurrent gout attacks: an Internet-based case-crossover study. *Am J Med* 2014;127:311–8.
34 Singh JA, Reddy SG, Kundukulam J. Risk factors for gout and prevention: a systematic review of the literature. *Curr Opin Rheumatol* 2011;23:192–202.
35 Menckeberg TT, Bouvy ML, Bracke M, *et al*. Beliefs about medicines predict refill adherence to inhaled corticosteroids. *J Psychosom Res* 2008;64:47–54.
36 BKF W, Cheung WHK, Ball PA. Beliefs about medicines among Hong Kong hospital outpatients. *Int J Pharm Pract* 2017;25:447–53.
37 De Vera MA, Marcotte G, Rai S, *et al*. Medication adherence in gout: a systematic review. *Arthritis Care Res* 2014;66:1551–9.
38 Kelly A, Tymms K, Wit M, *et al*. Patient and caregiver priorities for medication adherence in gout, osteoporosis, and rheumatoid arthritis: nominal group technique. *Arthritis Care Res* 2020;72:1410–9.
39 Garcia-Guillen A, Stewart S, Su I, *et al*. Gout flare severity from the patient perspective: a qualitative interview study. *Arthritis Care Res* 2020 (published Online First: 2020/10/08).
40 Lorig K, Ritter PL, Laurent DD, *et al*. Online diabetes self-management program: a randomized study. *Diabetes Care* 2010;33:1275–81.
41 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.
42 Liang N, Sun M, Sun R, *et al*. Baseline urate level and renal function predict outcomes of urate-lowering therapy using low doses of febuxostat and benzbromarone: a prospective, randomized controlled study in a Chinese primary gout cohort. *Arthritis Res Ther* 2019;21:200.
43 Stamp LK, Chapman PT, Barclay M, *et al*. Can we predict inadequate response to allopurinol dose escalation? analysis of a randomised controlled trial. *Rheumatology* 2018;57:2183–9.
44 Singh JA, Yang S, Saag KG. Factors influencing the effectiveness of allopurinol in achieving and sustaining target serum urate in a US Veterans Affairs gout cohort. *J Rheumatol* 2020;47:449–60.