DANISH MEDICAL JOURNAL

Original Article

Dan Med J 2021;68(11):A06210502

Patients with severe gout treated in mixed settings

Claus Rasmussen, Monica Bak Larsen & Asta Linauskas

Department of Rheumatology, North Denmark Regional Hospital, Hjørring, Denmark

Dan Med J 2021;68(11):A06210502

ABSTRACT

INTRODUCTION We aimed to investigate whether patients with a definite gout diagnosis who were treated in mixed real-life settings (various hospital departments or general practice) followed treatment recommendations.

METHODS We included all patients in the hospital's uptake area in 2015-2017 who had been diagnosed with gout after microscopy findings of urate crystals. Data regarding comorbidities and indications for urate-lowering therapy (ULT) were collected. The criteria for treatment success were a p-urate level < 6 mg/dl (< 0.36 mmol/l) or < 5 mg/dl (< 0.30 mmol/l) if tophi were present. All patients were followed up for 24 months.

RESULTS The study included 100 patients with a median age of 70 years, and 82% of patients were males. An indication for ULT was present in 99 patients and initiated in 79 patients. Fourteen of these 99 patients died within one year. For the remaining 85 patients, p-urate was measured, and the target was reached by 22 (26%) patients, not reached by 33 (39%) patients and not measured in 30 (35%) patients. Treatment success was positively associated with a written treatment plan in the rheumatology record after microscopy, initiation of ULT in the clinic, provision of a gout leaflet, a higher number of outpatient visits and non-smoking status.

CONCLUSIONS Many patients with crystal-proven gout did not receive ULT as recommended. Even if ULT was initiated, the p-urate level was monitored infrequently and the dose of ULT was not escalated when necessary. The best outcomes were associated with continued care in a rheumatology clinic.

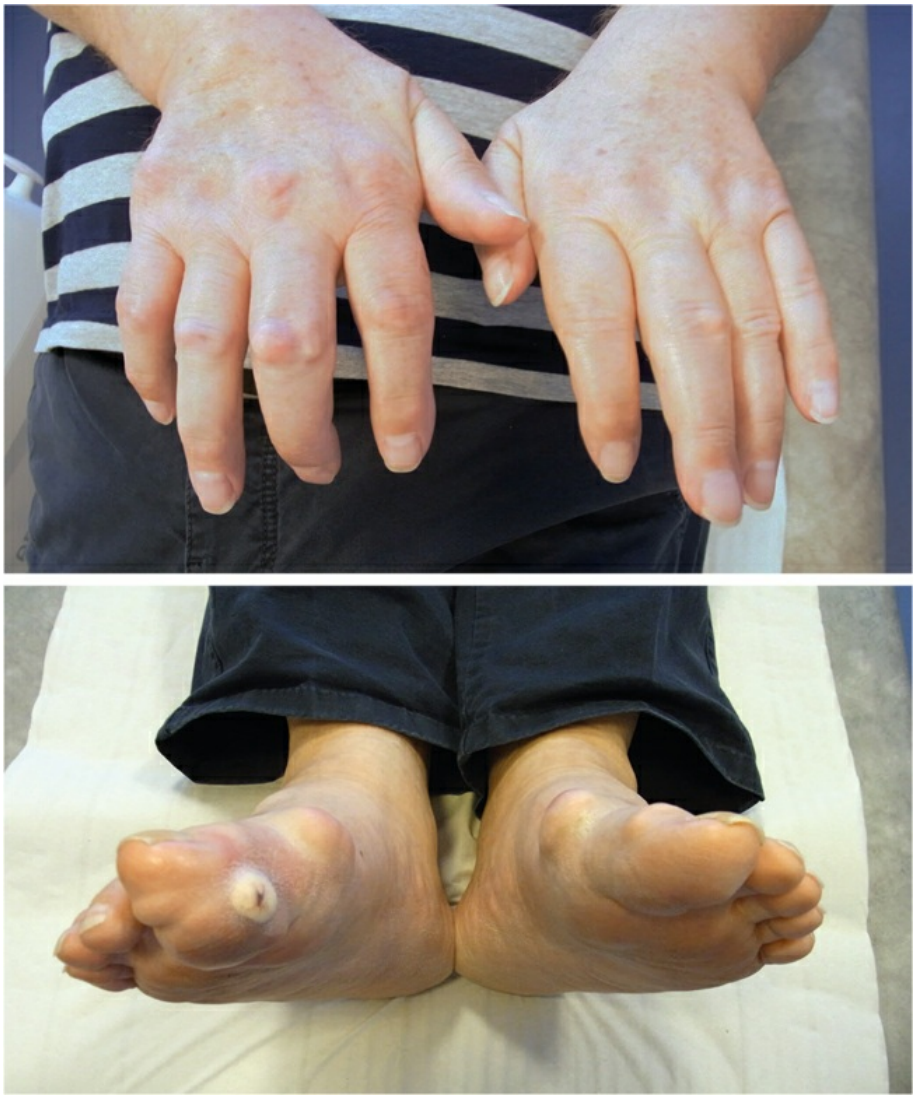
FUNDING none.

TRIAL REGISTRATION The study was assessed by the Ethics Committee, which decided it was a quality assurance project and the study was subsequently approved by the Regions data protection office service with ID 2018-62.

Gout is the most common inflammatory arthritis worldwide and its prevalence is increasing [1, 2]. Furthermore, gout and hyperuricaemia are associated with a low quality of life, comorbidities and increased mortality [3-6].

Due to suboptimal treatment of gout, recent guidelines have adopted the treat-to-target strategy, focusing on the steady reduction of tissue urate crystal deposition [7-9]. The importance of lifelong maintenance of a low plasma (p)-urate level (< 6 mg/dl (< 0.36 mmol/l)) is underlined. An even lower p-urate target level (< 5 mg/dl (0.30 mmol/l)) is recommended for patients with severe gout (tophi, chronic arthropathy and frequent attacks).

A wide consensus exists that urate-lowering drugs should be recommended to patients with established gout. Even so, studies from primary care show that less than half of patients receive urate-lowering therapy (ULT); moreover, in those who do receive ULT, the dose is usually fixed without titration to achieve a target serum urate concentration. Furthermore, treatment adherence is poor [10, 11].



A 60-year-old male with abundant urate deposits (tophi) after 20 years with undiagnosed gout and no urate-lowering therapy.

Previous studies have described treatment of patients with gout in either specialised rheumatology care or in primary care [11, 12]. We aimed to investigate whether patients with definite gout received the recommended treatment in real-life mixed settings (rheumatology clinics, emergency wards, other specialties and in general practice), and if not, to describe the factors associated with failure to reach the target serum urate concentration.

METHOD

Setting

This was a hospital-based prospective cohort study conducted in the Clinic of Rheumatology, North Denmark Regional Hospital, Denmark. The clinic provided a urate crystal microscopy service for all the hospital's clinical departments and for general practice in the entire uptake population (290,000).

Study population and gout diagnosis

Patients were referred for examination from general practitioners (GPs) or were examined (by consult) while they were stationary patients in other departments. Joint or tophus punctures were performed in the outpatient clinic by rheumatologists or specimens were sent from orthopaedic surgeons or cardiologists. All microscopies

were prospectively recorded in a local logbook, including date, puncture site and results. The cohort comprised all patients consecutively recorded in the logbook after microscopy with urate crystals in the rheumatology clinic in the period from 4 February 2015 to 16 June 2017.

Data acquisition

Baseline information was collected from the medical records of patients (**Table 1**). It was also assessed if a specified treatment plan had been noted in the hospital's medical record regarding flares, prophylaxis of flares, ULT and target p-urate value, as well as the discharge letter to the GP from the hospital including a plan for continuous ULT and monitoring. If several p-urate measurements had been performed 0-3 years before the date of diagnosis, the highest value recorded was used. Smoking status was dichotomised into current smoking or no smoking/ever/stopped. All prescribed treatments and subsequent pick-up of prescriptions in pharmacies were confirmed in the national database termed Shared Medicine Card.

TABLE 1 Baseline characteristics: status at the time of gout diagnosis with crystal detection by microscopy.

	Baseline
Patients, n	100
Males/females, n	82/18
Age, median (range), yrs	70 (20-98)
eGFR, median (range), ml/min.[a]	63 (14-121)
P-urate level, median (range)[b]	8.7 (5.5-16.3) mg/dl (0.54 (0.33-0.98) mmol/l)
Tophi, yes/no, n	32/68
Smoking, yes/no/missing, n	14/73/13
Alcohol > 6 U/wk, yes/no/missing, n	35/40/25
No comorbidity[c] related to gout, n [8]	5
Hypertension, n	67
eGFR < 60 ml/min., n	39
Atrial fibrillation, n	26
Any heart disease, n	49
Diabetes, n	16
Additional arthritis diagnosis, n	11
Additional comorbidity[d], n	69
Previous ULT, n	16
Puncture site for urate crystals, n:	
Knee	48
Ankle	7
Elbow	2
Wrist	3
Toe incl. 1st MTP joint	13
Finger	1
Tophus: skin, tendon, joint	24
Other	2

eGFR = estimated glomerular filtration rate; MTP = metatarsophalangeal; ULT = urate-lowering therapy.
a) 3 missing.
b) 2 missing.
c) Comorbidity related to gout: hypertension, impaired kidney function, any heart disease or diabetes.
d) Long-term treatment for another chronic medical condition not related to gout, e.g., osteoporosis or obstructive lung disease.

Outcome

The outcome measure was agreement with the national guideline for gout treatment, including initiation of ULT, monitoring of p-urate level and dose escalation as necessary to achieve the target p-urate level at a two-year follow-up in all patients who survived the first year after microscopy. For patients who died after 12 and before 24 months, the latest monitored p-urate level after 12 months was regarded as the two-year outcome.

Clinical consequences for follow-up after urate crystal detection by microscopy

The finding of urate crystals by microscopy with or without a treatment plan was noted in the joint medical

record of the hospital. After microscopy, the patients could be returned to the care of GPs or offered additional follow-up consultations in the rheumatology clinic. Patients who were stationary in another department at the time of microscopy relied on treatment in their stationary department, including orthopaedic surgery, emergency wards or internal medicine.

International and national guidelines for gout treatment

Treatment of attacks, prophylaxis and ULT were to comply with the national guideline published in April 2015 (available from the corresponding author) [9]. The Danish guideline from 2015 did not mention or specify how to refer patients from the rheumatology clinics (after the initial diagnosis and/or treatment) to ensure proper long-term follow-up in general practice, but this was subsequently added as part of a guideline update in March 2021 (Danish Society of Rheumatology).

Categorical data were compared using the chi-squared test or Fisher's exact test, and continuous data (age, doses of ULT, number of visits and number of months treated in the clinic) were compared using the Mann-Whitney test. The significance level was set to 5%.

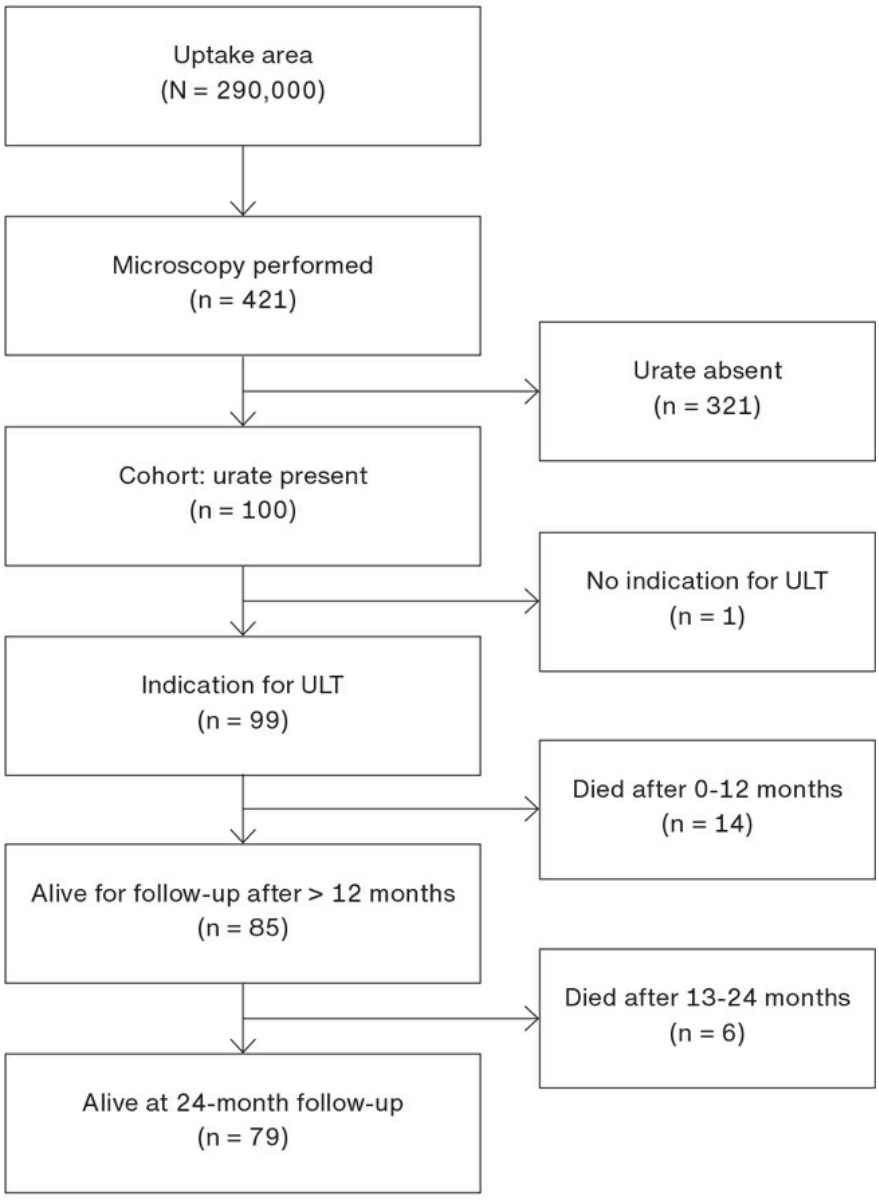
Trial registration: The study was assessed by the regional ethics committee as a quality assurance project and was thus subsequently approved by the regional data protection office with study ID 2018-62.

RESULTS

Study population and characteristics

In the period from 4 February 2015 to 16 June 2017, the clinic performed 421 microscopic joint fluid examinations, and only patients with birefringent urate crystals constituted our cohort (n = 100) (**Figure 1**). The prevalence of comorbidity was high, as shown in Table 1. A history of cancer was known in five patients. Overall, 20 patients died during the 24-month follow-up period, of whom 14 died during the first year. At least one clear indication for ULT was present in 99 patients according to both the national guideline and the European Alliance of Associations for Rheumatology (EULAR) recommendations. One patient suffered his first gout attack and had no comorbidity to give a clear indication for ULT.

FIGURE 1 Flow chart describing study population selection from the uptake area to formation of the cohort and the final follow-up visit.



ULT = urate-lowering therapy.

Initial treatment of flare and subsequent urate-lowering therapy with allopurinol or febuxostat

Eight patients had only joint fluid or tophus material sent for examination, and four (50%) of those patients were not otherwise seen in the clinic. An initial intra-articular steroid injection was given to 28 (28%) patients. Colchicine was used for both attacks (n = 69, 69%) and prophylaxis (n = 39, 39%). The initiation of ULT was stated in medical records or prescribed for 79 (80%) patients. ULT was initiated by a GP in four (20%) of 20 patients after discharge from the hospital.

In all cases, ULT was initiated with allopurinol 50-150 mg/day, and the intake of allopurinol and febuxostat could

be reliably assessed for the 85 patients surviving after one year until their two-year follow-up.

Due to side effects, six patients were switched from initial allopurinol to febuxostat. Overall, 62% (n = 8) of the patients with severe kidney disease (estimated glomerular filtration rate < 30 ml/min.) initiated and tolerated allopurinol treatment, and three (38%) of those patients reached the recommended treat-to-target value. No cases of allopurinol hypersensitivity syndrome were observed. Only allopurinol or febuxostat were used for ULT.

Empowerment at baseline of treat-to-target treatment

A written treatment plan was noted in the medical record after microscopy for each of the following phases: acute attacks (n = 71 (72%), flare prophylaxis (n = 46 (47%), ULT (n = 76 (77%) and a treat-to-target value for p-urate (n = 45 (45%). Information from the hospital to GPs about the gout diagnosis and a plan for recommended ULT was sent in 27 (27%) of 99 patients after discharge from the hospital or outpatient clinic.

Outcome expressed as monitored p-urate value and reached target p-urate value

Monitoring of the p-urate level at least once after the first year was accomplished in 55 (65%) of 85 patients, and the p-urate target level was reached by 22 (26%) patients; none of the 11 smokers in the study achieved the target level. Among the 32 (32%) patients with tophi at baseline, 24 (75%) patients survived after the first year, but only six (25%) of these patients reached a p-urate level below 5 mg/dl (0.30 mmol/l). In 33 (39%) patients, the p-urate level was measured and exceeded the target, but this did not trigger the recommended dose escalation. A total of 56 (66%) patients were treated with allopurinol 100-600 mg daily, and the median dose of allopurinol (300 mg) was significantly ($p < 0.001$) higher in the 20 (36%) patients who reached the target p-urate level than the median of level of 150 mg daily in the 36 (64%) patients who did not achieve the target p-urate level. Reluctance to escalate the dose of allopurinol or febuxostat could not be explained by either drug side effects or contraindications. The fixed dose of 80 mg febuxostat produced the target value in only two (40%) of five patients.

Treatment success could not be attributed to baseline comorbidity or indication for ULT. Furthermore, initiation of ULT and achievement of the target p-urate level and thus treatment success were associated with having a specified treatment plan in the hospital record at baseline, initiation of ULT in the clinic, sufficient increases in allopurinol/febuxostat doses, provision of a leaflet about gout at baseline, number of outpatient visits and non-smoking status (**Table 2**).

TABLE 2 Empowerment at baseline for initiation of urate-lowering therapy (ULT) in all 99 patients with an indication for ULT at baseline. Empowerment of ULT in the outpatient clinic: leaflet to patient, medical information in hospital files and to the general practitioner (GP) after discharge from hospital.

	ULT			
Empowerment of ULT in the outpatient clinic	not initiated (n = 20)	initiated (n = 79)	indication (N_{tot} = 99)	p-value[d]
Plan[a] for flare treatment, yes/no, n	11/9	63/16	74/25	0.002
Plan[a] for prophylaxis, yes/no, n	1/19	45/34	46/53	< 0.001
Plan[a] for ULT, yes/no, n	2/18	74/5	76/23	< 0.001
Plan[a] for stated treat-to-target p-urate level, yes/no, n	3/17	42/37	45/54	0.002
Recommendation[b] from clinic to GP about ULT, yes/no, n	2/18	25/54	27/72	0.052
Gout leaflet[c] provided, yes/no, n	1/19	41/38	42/57	< 0.001
Drug leaflet[c] provided, yes/no, n	1/19	38/41	39/60	< 0.001
Visits in outpatient clinic, median (range), n	1 (0-16)	5 (0-38)	4 (0-38)	< 0.001
Mos. treated in outpatient clinic, median (range), n	0 (0-24)	6 (0-24)	4 (0-24)	0.002
Type of 1st consultation, n:			< 0.001	
Rheumatology outpatient clinic	10	67	77	
Consults for other departments	4	10	14	
Only biomaterial examined	6	2	8	

a) A plan is written in the medical record covering the 4 phases: acute flare, prophylaxis, ULT, and treat-to-target value for p-urate level.
b) Recommendation to GP given after the last visit or discharge of the patient.
c) Leaflets about gout and all drugs used were readily available for handout in the outpatient clinic.
d) Not initiated versus initiated ULT.

DISCUSSION

This real-life study conducted in mixed clinical settings showed that only 80% of patients with definite gout initiated ULT as recommended. Among those who did initiate ULT, the p-urate serum level was not monitored in 23% of patients, and if it was monitored, the dose was not escalated in 55% of patients even though this was both necessary and possible. Comorbidities at baseline were present in 95% of patients, and the two-year mortality rate was 20%. Our findings indicate that the clinical real-life impact of guidelines published by rheumatology societies falls short of achieving a successful treat-to-target outcome. The clinical implications of finding urate crystals are not adequately acted upon. Unclear or insufficiently specified treatment plans in the medical records and discharge letters after microscopy may significantly contribute to the poor results. Sufficient doses of allopurinol were clearly associated with the achievement of the target p-urate level and doses could be escalated without significant side effects or allopurinol could be replaced by febuxostat.

The strengths of this real-life cohort study were that all patients had crystal-proven gout, were consecutively recruited and not selected among patients who had given their written informed consent to participate in a clinical study limited to a single setting. Thus, the study reflected real-life, long-term treatment conducted in the clinic and in emergency wards, other specialties and in general practice. A pervading consensus exists that life-long urate-lowering drugs should be recommended to patients with severe established gout whose flares are sufficiently severe for them to be admitted to the hospital. We included a complete two-year follow-up that encompassed all patients, even after referral back to general practice or treatment in other hospital departments.

The weaknesses were focused on outcome measures only, which consisted of ULT initiation, monitoring the p-urate level and reaching the target value. The number of flares and complications of gout were not assessed. Among the 20 patients who died during the follow-up period, 14 died within the first year when initiation of ULT and dose escalation were typically in progress. We acknowledge the provision of information to the patient and a specified treatment plan; both are baseline variables and not an intervention. However, we believe that the

written plan might likely have prompted other physicians later in the treatment course to follow the plan rather than making alternative prescriptions.

The poor result with only 26% of patients reaching the treat-to-target value is clearly inferior to the result reported in another Danish study [12] in which the author reported an 85% achievement of the treat-to-target value within a median of ten months in rheumatology care. However, our patient cohort was generally older (a median of seven years older), had more severe disease (50% more patients with tophi) and comprised fewer patients who had previously received ULT (70% fewer). In our study, we dichotomised our treat-to-target value as recommended, with a lower p-urate value required if tophi were present, and follow-up was also done after the patients had returned to GPs or other hospital departments.

The 20% share of patients who died within 24 months was much higher than the shares reported in other studies [5, 6, 12]. We cannot fully explain the statistically higher mortality rate in our study, but it indicates that our study population may be different, even though the studies were conducted within the same small country (Denmark) and apparently using the same selection criteria and treatment principles [12]. We included patients with urate crystal findings even though they relied on interventions from other hospital departments. We did not include patients with clinical gout but without crystal findings. One theoretical explanation for the observed higher mortality rate may be a higher level of cardiovascular comorbidity and a median 7-12 years' higher age at the time of gout diagnosis among the patients in the present cohort compared with the patients included in the three cited studies [5, 6, 12].

Addressing risk factors for hyperuricaemia (e.g., overweight, excessive alcohol intake and a high dietary intake of purines and fructose) is advised, but this rarely reduces plasma urate sufficiently to prevent the continuous deposition of urate [13]. This advice may even contribute to common misconceptions about gout (e.g., that it is self-limiting and not a serious disease and that it is self-induced by inexpedient lifestyle). These misconceptions are important barriers to optimal care [11].

The previous reluctance to use allopurinol close to flares and in a sufficient dose for patients with impaired kidney function was also questioned in well-designed studies [14]. The absence of the dose escalation necessary to achieve the target in our study cannot be explained by contraindications, but is more likely due to insufficient acceptance or understanding of the treatment principles among physicians. Currently, no national gout treatment guideline exists for treatment in general practice. Transfer from the clinic to the GP must thus be accompanied by a specified treatment plan to ensure long-term follow-up.

CONCLUSIONS

The clinical implications after findings of urate crystals are not adequately acted on. Our findings are in line with those of several other studies that have documented poor adherence to gout treatment guidelines.

Correspondence *Claus Rasmussen.* E-mail: clara@rn.dk

Accepted 1 September 2021

Conflicts of interest none. Disclosure forms provided by the authors are available with the article at ugeskriftet.dk/dmj

References can be found with the article at ugeskriftet.dk/dmj

Cite this as Dan Med J 2021;68(11):A06210502

REFERENCES

1. Kuo CF, 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. Zobbe K, Prieto-Alhambra D, Cordtz R et al. Secular trends in the incidence and prevalence of gout in Denmark from 1995 to 2015: a nationwide register-based study. Rheumatology 2019;58:836-9.
3. Annemans L, Spaepen E, Gaskin M et al. Gout in the UK and Germany: prevalence, comorbidities and management in general practice 2000-2005. Ann Rheum Dis 2008;67:960-6.
4. Kuo CF, Grainge MJ, Mallen C et al. Comorbidities in patients with gout prior to and following diagnosis: case-control study. Ann Rheum Dis 2016;75:210-7.
5. Perez-Ruiz F, Martínez-Indart L, Carmona L et al. Tophaceous gout and high level of hyperuricaemia are both associated with increased risk of mortality in patients with gout. Ann Rheum Dis 2014;73:177-82.
6. 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.
7. Sivera F, Andrés M, Carmona L et al. Multinational evidence-based recommendations for the diagnosis and management of gout: integrating systematic literature review and expert opinion of a broad panel of rheumatologists in the 3e Initiative. Ann Rheum Dis 2014;73:328-35.
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. Danish Society of Rheumatology. [National guideline for treatment of gout.] (In Danish). 2015. https://danskreumatologi.dk/nbv/sygdomme/artritis-urica/ (Sep 2020.)
10. Doherty M, Jansen TL, Nuki G et al. Gout: why is this curable disease so seldom cured? Ann Rheum Dis 2012;71:1765-70.
11. Dehlin M, Ekstrom EH, Petzold M et al. Factors associated with initiation and persistence of urate-lowering therapy. Arthritis Res Ther 2017;19:6.
12. Slot O. Gout in a rheumatology clinic: results of EULAR/ACR guidelines-compliant treatment. Scand J Rheumatol 2018;47:194-7.
13. Holland R, McGill NW. Comprehensive dietary education in treated gout patients does not further improve serum urate. Intern Med J 2015;45:189-94.
14. Stamp LK, O'Donnell JL, Zhang M et al. Using allopurinol above the dose based on creatinine clearance is effective and safe in patients with chronic gout, including those with renal impairment. Arthritis Rheum 2011;63:412-21.