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## **UltraSound Evaluation in Follow-up of Urate-Lowering therapy in gout phase 2**

### **(USEFUL-2): duration of flare prophylaxis**

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## Abstract

### OBJECTIVES

To determine whether changes in ultrasonography (US) features of monosodium urate crystal deposition is associated with the number of gouty flares after stopping gout flare prophylaxis.

### METHODS

We performed a 1-year multicentre prospective study including patients with proven gout and US features of gout. The first phase of the study was a 6-month US follow-up after starting urate-lowering therapy (ULT) with gout flare prophylaxis. After 6 months of ULT, gout flare prophylaxis was stopped, followed by a clinical follow-up (M6 to 12) and ULT was maintained. Outcomes were the proportion of relapsing patients between M6 and M12 according to changes of US features of gout and determining a threshold decrease in tophus size according to the probability of relapse.

### RESULTS

We included 79 gouty patients (mean [ $\pm$  SD] age  $61.8 \pm 14$  years, 91% males, median disease duration 4 [IQR 1.5; 10] years). Among the 49 completers at M12, 23 (47%) experienced relapse. Decrease in tophus size  $\geq 50\%$  at M6 was more frequent without than with relapse (54% vs 26%,  $P= 0.049$ ). On ROC curve analysis, a threshold decrease of 50.8% in tophus size had the best sensitivity/specificity ratio to predict relapse (AUC 0.649 [95% confidence interval 0.488 ; 0.809]). Probability of relapse was increased for patients with a decrease in tophus size  $<50\%$  between M0 and M6 (OR 3.35 [95% confidence interval 0.98; 11.44]).

### CONCLUSION

A high reduction in US tophus size is associated with lower probability of relapse after stopping gout prophylaxis. US follow-up may be useful for managing ULT and gout flare prophylaxis.

Keywords: ultrasonography, gout, prophylaxis, flare, urate lowering therapy, management

## **Introduction**

Gout is a joint disease characterized by deposition of monosodium urate (MSU) crystals in joints, tendons and/or soft tissues secondary to chronic hyperuricemia (1). A retrospective study of the association between serum urate (SU) level and recurrence of gouty arthritis showed reduced relapse rate during urate-lowering therapy (ULT) (2). The primary goal for ULT is to reduce and maintain SU level < 6 mg/dL (360 µmol/L) and < 5 mg/dL (300 µmol/L) with severe gout (3), with prevention of gout flare. Long-term achievement of low SU level results in decreased incidence or disappearance of gout flares and dissolution of tophaceous deposits (4). Thus, the gold standard for follow-up after ULT is the SU level.

However, recent studies showed that ultrasonography (US) could be useful for managing ULT in gouty patients (5–8). In the first phase of the present study (UltraSound Evaluation in Follow-up of Urate-Lowering therapy in gout phase 1 [USEFUL-1]), we suggested that US was an accurate tool to follow MSU crystal dissolution under efficient ULT, with disappearance of the “double contour” (DC) sign and reduction of tophus size. (8)The velocity of disappearance of US features of gout was correlated with the decrease in SU level.

For gout flare after starting ULT, prophylaxis is recommended during the first 6 months of ULT. Recommended prophylactic treatments are colchicine or low-dose non-steroidal anti-inflammatory drugs (NSAIDs) when colchicine is not tolerated or is contraindicated. The duration of gout flare prophylaxis over the 6 months is consensual with a grade B recommendation (3). However, little is known about the probability of relapse according to the urate load modification.

The aim of this second-phase study (USEFUL-2) To determine whether changes in US features of MSU crystal deposition is associated with the number of gouty flares after stopping gout flare prophylaxis.

## **Patients and methods**

### *Study design*

The design of the study was previously detailed (8). Briefly, we performed a 1-year prospective multicentre study (USEFUL study) involving gouty patients requiring ULT. Four centres in two countries (France and Lithuania) were involved.

The first phase of the study (USEFUL-1) was a 6-month US follow-up of MSU crystal deposition after the initiation of ULT. During this period, gout flare prophylaxis was co-prescribed with ULT as recommended (3,9,10). Two modalities of ULT were proposed to the physician: 1) allopurinol 100 to 900 mg/d according to kidney function or 2) febuxostat 40 to 120 mg/d. The SU target was at least a decrease  $< 360 \mu\text{mol/l}$ . For gout flare prophylaxis, the proposed therapies were colchicine, NSAIDs or corticosteroids, as recommended (3). US assessment was performed at baseline (M0) and at 3 months (M3) and 6 months (M6) after starting ULT.

After 6 months of ULT, gout flare prophylaxis was stopped. The second phase of the study (USEFUL-2) was a clinical follow-up (M6 to M12) after stopping gout flare prophylaxis with no US follow-up. At M9 and M12 after starting ULT, the occurrence, number and location of flares, and SU level were recorded. For gouty arthritis, flare was treated with colchicine, NSAIDs or corticosteroids. Relapse was considered if the patient had at least one flare after stopping gout flare prophylaxis. Flare was defined by the presence of at least 3 of 4 criteria (patient-defined gout flare, pain at rest  $> 3$  on a 0-10 numeric rating scale, presence of at least one swollen joint, presence of at least one warm joint) as described by Gaffo *et al* (11,12).

### *Patient selection*

To be included in the USEFUL study, patients had to be  $> 18$  years old, provide informed consent, have proven gout by the identification of MSU crystals in synovial fluid (13,14), show

US features of gout at M0 (at least one US feature of gout [DC sign and/or tophus] in at least one joint site [knees and/or first metatarsophalangeal joints (MTP1s)] and have no history of ULT. Exclusion criteria were 1) corticosteroid injection into knees or MTP1s within the previous 3 months, 2) presence of knee prosthesis or hallux valgus surgery, 3) under ULT, and 4) no possibility to follow the patient for 1 year.

At M0, all patients underwent a detailed clinical evaluation, including disease history (disease duration, number of gout flares), clinical examination (age, sex, presence of clinical tophi (tophi revealed by clinical exam), body mass index), and laboratory testing (SU and serum creatinine levels [allowing for determining estimated glomerular filtration rate (eGFR) according to the Modification of Diet in Renal Disease study formula]. SU level was assessed at M3, M6, M9 and M12 after ULT initiation.

#### *Ethical statement*

The Institutional Review Board (IRB No. 00006477) of Paris North Hospitals and the Biomedical Research Ethics Committee of the Lithuanian University of Health Sciences Kaunas Region reviewed and approved this study. All patients gave their written informed consent to participate.

#### *Outcomes*

The primary outcome of USEFUL-2 was the proportion of patients showing relapse of gout arthritis between M6 and M12 according to the modification of the two US features of gout (DC sign and tophus). Secondary outcomes were 1) determining a threshold decrease in tophus size according to relapse and 2) the number of flares in relapsing patients according to US outcome.

### *Statistical analysis*

Continuous variables are expressed as mean $\pm$ SD or median [interquartile range (IQR)] and were compared by Wilcoxon rank sum test. Categorical variables are expressed as number (%) (percentages were calculated excluding missing data) and were compared by chi-square test or Fisher's exact test, as appropriate. We calculated 95% confidence intervals (95% CIs) by the Wilson method. The threshold of percentage decrease in tophus size according to relapse at M12 was determined by receiver operating characteristic (ROC) curve analysis, with the best sensitivity and specificity (maximal Youden's index). For all analyses,  $P < 0.05$  was considered statistically significant. Because of the exploratory character of the comparisons, the type I error was not adjusted for multiplicity. All statistical analyses involved use of SAS 9.4 (SAS Inst., Cary, NC).

## Results

### *Characteristics of the population at M0 (Table 1)*

A total of 79 patients with gout (mean [ $\pm$  SD] age  $61.8 \pm 14.0$  years, 91% male) were included (Table 1). The median disease duration was 4 [IQR 1.5; 10] years. Clinical tophi were found in 23 (29.1%) patients. The mean baseline SU level was  $530 \pm 97$   $\mu\text{mol/l}$  ( $8.9 \pm 1.6$  mg/dL).

Allopurinol and febuxostat were started in 26 (33%, mean dose  $125 \pm 43$  mg/d) and 53 (67%, mean dose  $65.7 \pm 19.4$  mg/d) patients, respectively. For gout flare prophylaxis, colchicine was started in 70 (88.6%) patients (mean dose  $0.6 \pm 0.3$  mg/d). NSAIDs and corticosteroids were given to 8 (10.1%) and 1 (1.3%) patients, respectively.

### *Characteristics of M6 and M12 completers (Table 1)*

A total of 49 patients (62%) were completers at M6 and M12. The whole population and M6-M12 completers did not differ in clinical and US characteristics (Table 1). Among the 49 M6-M12 completers, 47 (95.9%) and 45 (91.8%) had at least one US tophus or DC sign, respectively.

### *Primary outcome: association of stopping gout flare prophylaxis with relapse (Table 2)*

Among the 49 M6-M12 completers, 23 (47%) had at least 1 relapse after stopping gout prophylaxis, corresponding to 13 (49%) of the 47 patients with at least one US tophus at M0 and 23 (51%) of the 45 patients with at least one DC sign at M0.

Among the 47 patients with tophus at M0, the tophus size at M0 did not differ with or without relapse (Table 2). The mean percentage decrease in tophus size at M6 was lower - but not significantly- with than without relapse ( $-36.0 \pm 31.2\%$  vs  $-54.1 \pm 34.2\%$ ,  $P=0.082$ ). The absolute decrease in tophus size without and with relapse was  $-6.3 \pm 4.4$  and  $-4.3 \pm 3.2$  mm, respectively ( $P=0.1$ ). Decrease in tophus size  $\geq 50\%$  at M6 was more frequent without than with relapse (54% vs 26%,  $P= 0.049$ ). The final median size of tophus at M6 was greater with



than without relapse (10 [IQR 6; 13] vs 5 [2; 9] mm,  $P=0.024$ ). SU levels at M12 did not differ between patients having a reduction  $>50\%$  of their tophus size and those without.

For the DC sign, disappearance of US features at M6 was not associated with reduced relapse; neither SU levels (Table 2).

*Secondary outcome: determining a threshold decrease in US tophus size by probability of relapse*

On ROC curve analysis (Fig. 1), a threshold decrease of 50.8% in tophus size between M0 and M6 had the best sensitivity/specificity ratio (78%, 95% CI [56; 93]/54%, [33; 74]). Probability of relapse was increased for patients with a decrease in tophus size  $<50\%$  between M0 and M6 (odds ratio 3.35 [95% CI 0.98; 11.44]).

*Secondary outcome: number of relapses*

Among the 23 relapsing patients, the mean number of relapses was  $3.1 \pm 2.9$  ( $n=17$  patients) and  $2.0 \pm 2.4$  ( $n=6$  patients) with a tophus size reduction  $<$  and  $\geq 50\%$ , respectively ( $P=0.09$ ). For the DC sign, the disappearance of US features was not associated with number of relapses. Among the 23 patients with total disappearance of DC sign, 11 experienced a flare (mean of  $2.8 \pm 2.8$  flare/patient). Among the 15 patients with absence of dissolution of DC sign, 8 experienced a flare (mean of  $2.9 \pm 2.9$  flare/patient).

Regarding ULT, there was no difference between allopurinol and febuxostat for number of relapse ( $3.3 \pm 3.2$  vs  $2.5 \pm 2.1$ ,  $P=0.6$ ).

## Discussion

ULT and treatment of flares are the two cornerstones of gout management. Introducing ULT also requires gout flare prophylaxis. At least 6 months' prevention with colchicine or NSAIDs is recommended by EULAR (3). ACR recommends to continue the prophylaxis for the greater of 6 months' duration, 3 months after achieving the target SU level for the patient without tophi detected on physical examination, or 6 months after achieving the target serum urate level, where there has been resolution of tophi previously detected on physical examination (15). However, this recommendation is consensual and we lack data on the duration of such prophylaxis in gout. In this second phase of the USEFUL study, we aimed to determine To determine whether changes in US features of MSU crystal deposition is associated with the number of gouty flares after stopping gout flare prophylaxis.

We found that relapsing-patients had less of a decrease in tophus size. Probability of relapse was increased with a reduction in tophus size <50%. Additionally, the tophus size at the end of gout flare prophylaxis could predict the probability of relapse. This is the first study demonstrating an association between changes in US features of gout and relapse after stopping gout flare prophylaxis. The results suggest that US monitoring of tophus size might be helpful for close management of gout flare prophylaxis.

A recent study by Pascart *et al.* evaluated the correlation between baseline urate load measured by US and dual energy-CT (DECT) and relapse (16). As in our study, the authors found no association between DC sign and relapse. Baseline tophus size by DECT of the feet was the only marker associated with relapse. However, the study design was different, with the analysis of baseline US features without an analysis of modifications of urate load under ULT (16).

In our study, almost half of patients had at least one relapse during the 6-month follow-up after stopping prophylaxis. This high prevalence of flare agrees with previous literature. Indeed, in some studies, during the first month free of gout flare prophylaxis, up to 15% of patients

experience relapse (17–19). In the FACT study, 1 year after introducing ULT, 60% to 70% of patients had at least one relapse (20).

Surprisingly, we did not find probability of relapse associated with SU level at baseline or during follow-up. The literature on SU levels and probability of relapse in gout is contradictory. Shoji *et al.* showed that the prevalence of gout flare was correlated with an average SU measurement but not SU level at one time (2). In this 3-year retrospective study, the authors demonstrated that the incidence of gouty attacks was associated with lower SU levels (2). These data might suggest that differences in flare rates between ULT and placebo may become more distinct with longer-term therapy. In a retrospective study, Sarawate *et al.* found significantly fewer flares for patients on allopurinol with low SU than high SU level (21). However, another study (20) found that despite a different proportion of patients achieving a SU target <6.0 mg/dl after 1 year of allopurinol or febuxostat, the same proportion of patients experienced at least one relapse (64% and 70%, respectively). Based on aggregate clinical trial-level data, Stamp *et al.* did not confirm the association between SU and gout flare (22). These data suggest that SU level might not be sufficient to predict flares. SU levels measured at one time may not reflect exactly the urate load.

To measure urate deposition, US may be useful. Previous studies (6,7,23,24) suggested that US can show modification of urate deposition under efficient ULT. In the first phase of the USEFUL study, we showed a decrease in US features of gout, the DC sign and US tophus, associated with a decrease in SU levels under ULT (8). In this study, DC sign seemed an early marker of response (present at M3) to treatment and tophus size a later marker. In the second part of the study, we suggest that after stopping gout flare prophylaxis probability of relapse is low with a 6-month decrease in US tophus size  $\geq 50\%$ . In light of these results, US follow-up could be useful in the management of gout. In patients with US features of gout, we suggest searching for DC sign disappearance after 3 months (monitoring ULT dose and adherence) and

a decrease in tophus size after 6 months to monitor gout flare prophylaxis and ULT posology. Prophylactic treatment could possibly be maintained up to a reduction of > 50% of US tophus size. However, further prospective analysis will be needed to compare prophylactic strategy according to the evolution of tophus size, before changing our therapeutic strategy.

Our study has some limitations. First, 38% of patients did not complete the study, but this proportion of non-completers is expected among a usually well-known non-adherent population (25). In addition, our study design did not include strict recommendations for gout flare management. We have no data on adherence to gout flare prophylaxis. We cannot exclude that patients with a greater decrease in tophus size had a better adherence to ULT and also gout flare prophylaxis. Regarding definition of flare, self-reporting is very challenging. Categorisation of flare data may not capture the severity, duration or impact of flares. Different types of flare could be observed in our relapsing patient (26). Additionally, the association between risk of relapse and decrease of tophus size is only significant when the decrease was >50% suggesting a lack of power of our study and/or an absence of linear correlation. Moreover, we did not analyse US features at M12. Indeed, due to the correlation between decrease of tophus and SUA level observed in the first phase of the study (8), we stated that there would be a continuous decrease between M6 and M12. Thus, we thought that US assessment at M12 would not add any supplementary information. Finally, we did not compare US with other imaging modalities such as DECT. To better understand the impact of US on ULT management and the exact clinical relevance of such US follow-up, a prospective randomized control trial should be performed.

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Table 1: Baseline (M0) characteristics of all patients with gout and study completers at month 6 and 12 (M6-M12).

Baseline (M0) characteristics	All patients (M0) N=79	M6-M12 completers N=49	Drop-out patients N=30
Age, years	61.8 ± 14	62.0 ± 13.1	61.4 ± 15.8
Sex, n (% of males)	72 (91.1)	45 (91.8)	26 (86.7)
Cardiovascular diseases, n (%)	29 (36.7)	19 (38.8)	10 (33.3)
Hypertension, n (%)	53 (67.1)	34 (69.4)	19 (63.3)
Diabetes mellitus, n (%)	14 (17.7)	10 (20.4)	4 (13.3)
Dyslipidemia, n (%)	24 (30.4)	12 (24.5)	12 (40.0)
BMI, kg/m <sup>2</sup>	27.8 ± 5.1	27.3 ± 4.7	28.8 ± 5.7
Diuretic use, n (%)	35 (44.3)	23 (46.9)	12 (40.0)
- thiazides	16 (47.8)	10 (45.5)	6 (50.0)
- loop	21 (61.8)	13 (59.1)	8 (66.7)
Disease duration, years, median [IQR]	4 [1.5; 10]	4 [1 ; 10]	4 [2 ; 11]
No. of flares, median [IQR]	5 [3 ; 15]	5.5 [3 ; 12]	5 [3 ; 16]
Clinical tophus, n (%)	23 (29.1)	15 (30.6)	7 (23.3)
eGFR, ml/mn/1.73m <sup>2</sup>	60.8 ± 25.3	59.0 ± 24.0	62.9 ± 27.6
SU level, µmol/l	530.4 ± 97.2	517.4 ± 84.7	555 ± 112
mg/dL	8.9 ± 1.6	8.7 ± 1.5	9.3 ± 1.9
Gout prophylaxis			
- Colchicine, n (%)	70 (88.6)	40 (81.6)	29 (96.6)
- NSAIDs, n (%)	8 (10.1)	7 (14.3)	1 (3.3)
- Corticoids, n (%)	1 (1.3)	1 (2.0)	0
US sign			
- Double contour, n (%)	68 (86.1)	45 (91.8)	23 (76.7)
- Tophus, n (%)	74 (93.7)	47 (95.9)	26 (86.7)

Data are mean ± SD unless indicated

IQR: interquartile range; BMI: body mass index; eGFR: estimated glomerular filtration rate (according to Modification of Diet in Renal Disease study formula); SU: serum urate; NSAIDs, non-steroidal anti-inflammatory drugs; US, ultrasonography

Table 2: Characteristics of US findings and SU level by relapse status after stopping prophylaxis

	No relapse	Relapse	P
<b>US tophus at M0, n</b>	N=24	N=23	
Tophus size at M0, mm	12.0 ± 3.8	13.4 ± 5.9	0.343
Change in tophus size, mm	-6.3 ± 4.4	-4.3 ± 3.2	0.128
Decrease in tophus size, %	-54.1 ± 34.2	-36.0 ± 31.2	0.082
Decrease ≥50% in tophus size at M6, n (%)	13 (54)	6 (26)	<b>0.049</b>
Tophus size at M6, mm	5.6 ± 4.7	9.2 ± 5.6	<b>0.025</b>
	5 [2; 9]	10 [6; 13]	
<b>DC sign at M0, n</b>	N=22	N=23	
DC sign disappearance at M6, % of joints	63.3 ± 46.1	61.6 ± 43.4	0.853
<b>Patients with SU measurements, n</b>	N=26	N=23	
SU level at M0, μmol/L	517 ± 90	518 ± 81	0.82
mg/dL	8.7 ± 1.5	8.7 ± 1.4	
SU level at M6, μmol/L	289 ± 100	297 ± 70	0.68
mg/dL	4.9 ± 1.7	5.0 ± 1.2	
SU level at M12, μmol/L	270 ± 90	295 ± 100	0.36
mg/dL	4.5 ± 1.5	5.0 ± 1.7	
SU level < 360 μmol/L (ie <6mg/dL) at M6, n (%)	22 (85)	20 (87)	1.00

Data are mean ± SD and median [IQR] unless indicated.

DC: double contour; SU: serum urate

## **Figures Legend**

*Figure 1: Percentage of decrease of tophus and risk of relapse: ROC curve.*

*Figure 1 legend : In the completer population, AUC was 0.649 95%CI [0.488 ; 0.809]. The best ratio sensitivity/specificity was for a threshold of -50.83% of decrease of tophus size. The sensitivity was 0.783 [0.563 ; 0.925] and the specificity was 0.542 [0.328 ; 0.744].*

ROC curve

