gout, urate, and crystal deposition disease

MDPI

Perspective

Can Urate Lowering Therapy Be Stopped in Gout? Rationale and Design of Two Large Randomised Trials

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Abstract: Lifelong urate-lowering therapy (ULT) is recommended for gout to prevent flares and urate deposition. However, concerns about its adherence, long-term side effects, and the necessity of continuous treatment after achieving remission raise critical questions. Two randomised controlled trials (RCTs), GO TEST Finale and STING, aim to evaluate the safety and feasibility of ULT discontinuation in gout patients in remission. The GO TEST Finale is a superiority trial involving 310 patients in the Netherlands, comparing a treat-to-target (T2T) ULT continuation strategy with ULT discontinuation. Patients in the discontinuation arm resume ULT only after flare recurrence or tophi development. The primary outcomes focus on remission criteria failure over 24 months, while the secondary outcomes explore predictors of successful discontinuation and cost-effectiveness. The STING study, a non-inferiority trial in France, includes 450 patients without ultrasound (US) evidence of urate deposits. Patients in the discontinuation group resume ULT if a US detects urate deposition during follow-up, minimising flare risk. The primary outcomes measure the proportion of patients experiencing flares at two years, with the secondary outcomes examining the long-term health impacts and cost-effectiveness. These trials provide an opportunity for translational research into the immunological and epigenetic effects of rising serum urate levels. The results could inform personalised strategies for a drug-free period and address the critical question of whether lifelong ULT is necessary for gout management. The complementary findings from both trials are expected to contribute significantly to resolving this ongoing clinical debate.

Keywords: gout; urate lowering therapy; trial; urate; ultrasound

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1. Introduction

The European and American Societies of Rheumatology recommend lifelong urate-lowering therapy (ULT) for patients with gout to prevent the risk of de novo crystallisation and the recurrence of flares [1–3]. However, lifelong treatment raises the question of the long-term risk–benefit ratio, which is unknown in gout. Although the xanthine oxidase inhibitors allopurinol and febuxostat are generally well tolerated, they can cause side effects and require regular laboratory monitoring [4–6]. The adherence to lifelong ULT has been shown to be an important issue in clinical practice, with more than half of patients discontinuing treatment within the first 5 years. [7,8]. An important question underlying

these issues is whether patients should continue their ULT treatment for life once the target is achieved and gout symptoms have resolved. Or is it possible to stop ULT treatment or switch to a less stringent serum urate (SUA) target? To answer these questions, it is necessary to have a clear idea of the risks and benefits of the different strategies currently in use.

At the time of their elaboration, the EULAR recommendation to maintain ULT lifelong was justified by the fear of a possible deleterious effect of hyperuricemia on renal function and the cardiovascular system. However, since then, large randomised controlled trials [9–11] and Mendelian randomisation studies [12] have shown that high serum urate is not causally associated with increased cardiovascular or renal risk. The lifelong maintenance of ULT in gout patients is therefore justified only if its discontinuation leads to a recurrence of flares and, ultimately, to tophi and urate arthropathy.

Very few studies have assessed the risk of flares after discontinuing ULT. The most important withdrawal study in gout is a single case series of 211 patients in whom ULT was discontinued after 5 years of treatment: 38.9% had a crystal-proven recurrence of gout during a mean follow-up of 33.1 +/− 22.6 months. The cumulative recurrence rates at 1, 2, 3, and 4 years were 6.6%, 11.4%, 20.4%, and 29.4%, respectively [13], with flares generally occurring at the first metatarsophalangeal (MTP1) site.

The rate of flares was associated with the mean SUA after ULT withdrawal. Although the majority of patients re-developed hyperuricemia, 27 of 221 patients (13%) with an average SUA below 7.0 mg/dL (0.42 mmol/L) remained flare-free during follow-up. This study did not provide information on the presence or absence of MSU crystals at the time of ULT discontinuation, and patients were not monitored by ultrasound (US). An analysis of individual data from large cohorts of patients with asymptomatic hyperuricemia also showed that serum urate is a strong non-linear concentration-dependent predictor of incident clinical gout. However, the risk of gout in hyperuricemic patients is very low: at 3 years, the cumulative incidence (95%CI) ranged from 0.92% (0.49 to 1.36) for baseline serum urate levels of 7.0–7.9 mg/dL to 4.0% (2.59–5.40) for urate levels of 8.0–8.9 mg/dL. Only half of the patients with serum urate concentrations ≥10 mg/dL develop clinically evident gout over 15 years [14,15]. However, the risk of gout is likely to be much higher in patients who have had gout in the past.

A systematic review of the studies of ULT discontinuation showed that the relapse rates of gout are 36–81% and occur 1–4.5 years after ULT discontinuation. This means that some patients do not appear to experience gout flares after ULT discontinuation, while others present with severe disease after a variable period of time [16].

These results have led to the hypothesis that a drug-free period may be feasible in gout patients who no longer have flares and clinical and/or imaging evidence of urate deposition.

Two upcoming multicentre randomised trials will compare the continuation and discontinuation of ULT in gout patients in remission: the GO TEST Finale, conducted in the Netherlands, and STING, conducted in France (Table 1).

Table 1. The GO TEST Finale and the STING trials.

	GO TEST Finale	**STING**
Type	Open-label RCT	Open-label RCT
Design	Superiority design, 1:1 randomisation	Non-inferiority design, 1:1 randomisation
Patients	Gout according to the 2015 ACR/EULAR criteria, and in remission for at least 12 months	Gout according to the 2015 ACR/EULAR criteria, in remission for at least 24 months and no evidence for urate deposits on US

Table 1. *Cont.*

	GO TEST Finale	STING
Sample size	310 patients	450 patients
Interventions	T2T continuation of ULT	Withdrawal of ULT with bi-annual ultrasound scan. ULT resumed as soon as US shows urate deposits
Control	Discontinuation (with restart based on flares/tophi)	Maintenance of ULT
Duration	2 years *	3 years
Primary outcome	Failure to fulfil modified version of the preliminary remission criteria for gout in last 6 months follow up **,#	Proportion of patients experiencing one or more flares # at two years
Recruitment period	February 2021–June 2023	Not yet recruiting
Expected results	End of 2025	
Funding	ZonMW (governmental grant)	National hospital clinical research programme (governmental grant)

* with a 3-year extension possibility. ** no tophi, no gout flares, numeric rating scale (NRS) pain due to gout <2, and NRS gout disease activity <2 over the last 6 months of 24-month follow-up (sU excluded from the preliminary remission criteria). # flares will be assessed in both studies using Gaffo's definition.

2. The GO TEST Finale Study

The GO TEST (GOut TrEatment STrategy) Finale study is an ongoing, pragmatic, open-label, multicentre, randomised trial in gout patients in remission. The aim of the study is to demonstrate the superiority of a treat-to-target (T2T) ULT continuation strategy compared to a ULT discontinuation strategy in gout patients in remission. The rationale and design of the study were published in detail in 2023 [17].

The study population was recruited from the rheumatology departments of nine centres in the Netherlands. The main study centre (Sint Maartenskliniek) also acted as a referral centre for other hospitals and regional primary care practises. The inclusion period was between February 2021 and July 2023, and 310 patients were included, which met the pre-calculated sample size.

The eligibility criteria were as follows: gout patients aged 18 years or older, on active treatment with ULT (allopurinol, febuxostat, and/or benzbromarone) and fulfilling the preliminary gout remission criteria [18] with a modification regarding the timing of the pain and disease activity scoring (only at baseline) (see Table 2).

Table 2. Inclusion criteria regarding the definition of remission at baseline.

Inclusion Criteria	GO TEST Finale	STING
Gout flares	No flare in the past 12 months	No flare in the past two years
Tophi	No visible tophi during a physical examination in the past 12 months	NA
SUA target	All known SUA values of the past 12 months <6 mg/dL (<0.36 mmol/L)	SUA ≤6 mg/dL
Pain due to gout	NRS-score * of <2 at baseline	NA
Patient global assessment of gout disease activity	NRS score of <2 at baseline	NA
US evidence of depositions	NA	No urate deposits on US at both MTP1s and knees

NRS—11-point numeric rating scale, where 0 represents the best value and 10 the worst value. NA—not applicable.

The patients (n = 310) were randomised 1:1 to intervention or control. In the intervention group, patients continued their ULT according to a T2T strategy with a target SUA

level between 3.34 mg/dL (0.20 mmol/L) and 6 mg/dL (<0.36 mmol/L). Visible tophi at baseline were an exclusion criterion.

In the control group, the dose of ULT was tapered according to a predefined tapering schedule and stopped after zero to six weeks, depending on the baseline dose [17]. In the event of recurrent or persistent flares or the development of tophi after the discontinuation of ULT, ULT is restarted at the same dose as at study entry. Thereafter, (re-)treatment will continue similar to the T2T strategy used in the intervention arm.

Regular visits are planned at the baseline, 12 months and 24 months. The gout flare questionnaire is assessed monthly and additional questionnaires, regarding medical care consumption (institute for Medical Technology Assessment –iMTA-) and productivity loss (iMTA) are assessed every three months (Figure 1).

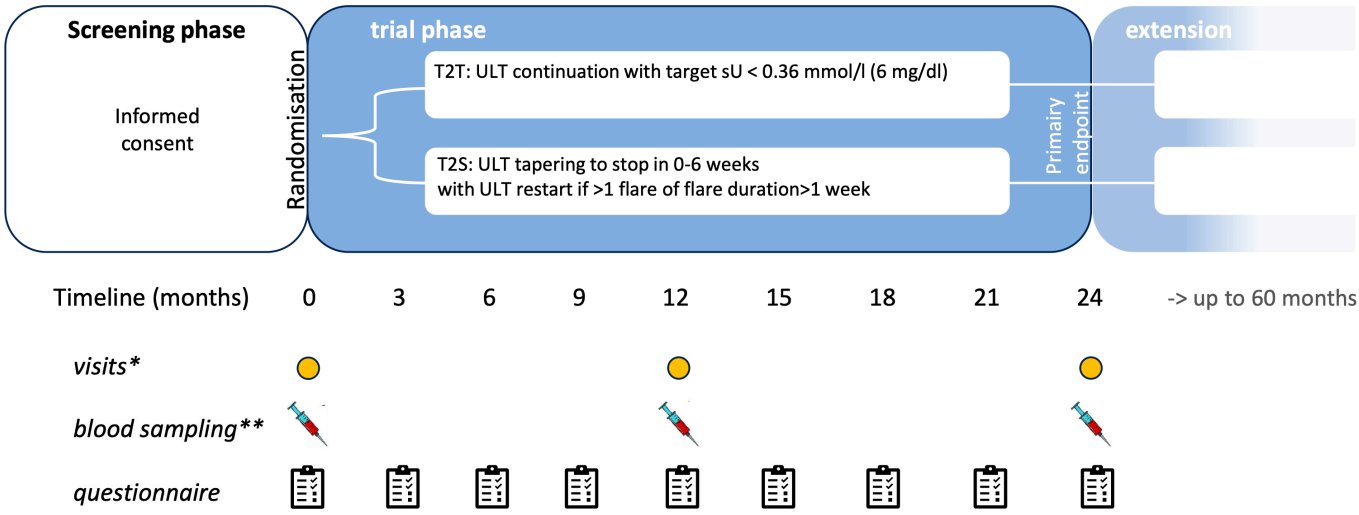

Figure 1. Study design of the GO TEST Final trial. * extra flare-confirmation visits on indication. ** blood sampling in the T2T-group two weeks after initial stop of ULT.

The primary outcome is the between-group difference in the proportion of patients not fulfilling the preliminary remission criteria for gout (excluding the serum urate criteria), during the last 6 months of the 24-month follow-up period. Flares are defined according to Gaffo's definition of gout flare, as stated above [19]. In case of doubts, an additional outpatient visit with a physician is scheduled for a clinical evaluation of the possible flare.

Secondary objectives include the assessment of the predictors (clinical, radiological, immunological and genetic variables) of a successful ULT discontinuation, the incidence of gout flares during the entire 24-month follow-up, the reintroduction or adjustment of ULT, the use of anti-inflammatory drugs, the cost-effectiveness of both strategies and the occurrence of adverse events, with a particular interest in cardiovascular and renal events.

3. The STING (Stop Treatment IN Gout) Study

The objective of the STING (Stop Treatment IN Gout) study (not yet recruiting) is to demonstrate that oral ULT withdrawal in patients with gout in remission, monitored with repeated US scans, is not inferior to maintaining oral ULT for the risk of flares at 2 years. It is a national, multicentre study involving 27 centres across France. Overall, STING will assess the feasibility of a drug-free period for people with gout who no longer have urate deposition.

The recruited and randomised population (n = 450) will consist of gout patients considered to be in remission [20] according to the following criteria: no flares for 2 years, SUA levels < 6 mg/dL (<0.36 mmol/L), ULTs taken for at least 2 years and no urate deposits on US at both MTP1s and knees. The absence of urate deposition is defined

as grade 0 according to the semi-quantitative ultrasound scoring system for gout lesions developed by OMERACT [21]. This population is therefore at a very low risk of developing flares [22] in the short to medium term when SUA levels rise after the cessation of ULT, similar to patients with asymptomatic hyperuricemia.

The patients will be randomised to (i) a maintenance group—where ULT will be continued—or (ii) an experimental withdrawal group—where ULT will be discontinued (Figure 2). The patients randomised to the discontinuation experimental group will resume ULT (SUA target below 6 mg/dL), which was stopped at D0, if a US performed during follow-up shows urate deposition (DC sign or tophi grade ≥2). This strategy will dramatically reduce the risk of flares in this group.

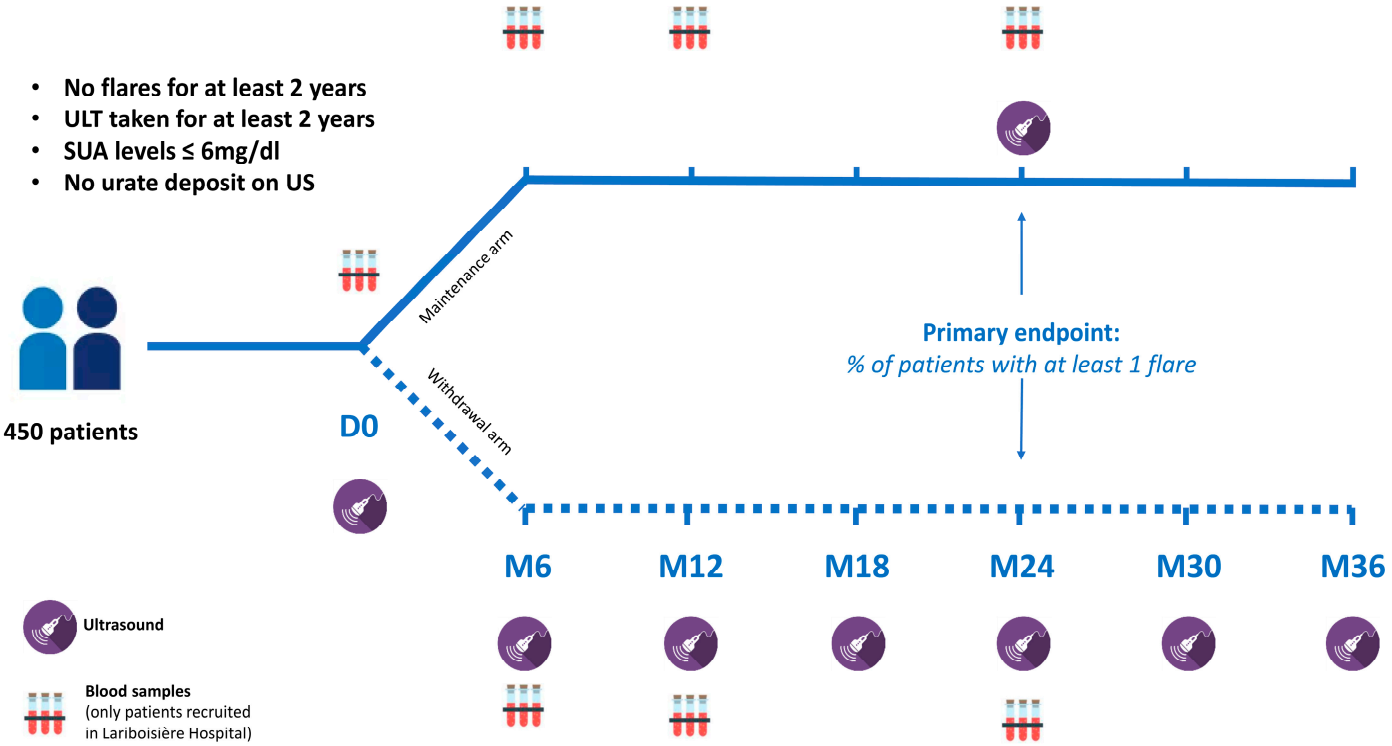

Figure 2. Study design of STING.

The primary endpoint is the proportion of patients experiencing one or more flares at two years (M24), defined according to the validated Gaffo's definition for gout flare. This requires meeting three out of the following four criteria endorsed by OMERACT: patient-defined gout flare, a pain at rest score >3 on a 0–10 numeric rating scale, the presence of at least one swollen joint, and the presence of at least one warm joint [19].

The secondary objectives include the following: the proportion of patients experiencing one or more flares and the mean flare rates; the incidence of ultrasound features of gout; the OMERACT core outcome domains for long-term gout studies; the incidence of major cardiovascular events, comorbidities, and mortality; the tolerance and adverse effects of medications; the adherence to urate-lowering therapy; the cost-effectiveness of ULT withdrawal monitored with US; flares will be recorded using two methods: a self-reported physical notebook completed by the patient and bi-monthly phone calls to ensure flare diaries are updated or to directly document flares, if any.

In each centre, ultrasound evaluations will be conducted by a designated rheumatologist with extensive experience in musculoskeletal ultrasound. The scanning protocol will cover the following sites: both first metatarsophalangeal joints (MTP1s) and both knees,

as these sites show the highest prevalence of deposits in asymptomatic hyperuricemic patients [23,24].

The ultrasound features to be recorded include the following:

At the MTP1s: the double contour (DC) sign, tophi, and aggregates.

At the knees (femoral condyles): the DC sign.

These features have been selected due to their high prevalence and discriminatory value in distinguishing individuals with asymptomatic hyperuricemia from normouricemic individuals [24].

4. The Two Studies Side by Side

Both trials are investigating the effect of stopping ULT in gout patients in remission on the risk of recurrence of gout signs and symptoms. A summary of the two studies' characteristics is provided in Table 1. The GO TEST Finale was designed to demonstrate the superiority of the ULT continuation strategy over the ULT discontinuation strategy. By contrast, the STING study is designed as a non-inferiority trial of ULT discontinuation compared to ULT continuation, exploring the feasibility of a drug-free period with US monitoring every six months.

Both studies differ in terms of the criteria for reintroducing ULT in the discontinuation arm. In the GO TEST Finale, ULT is restarted based on the recurrence of flares or the appearance of tophi, whereas in the STING trial, the decision to restart ULT relies on US evidence of crystal reappearance, aiming to avoid the risk of flares.

Additionally, the differences in inclusion criteria (Table 2) may result in distinct patient selection frameworks. In the GO TEST Finale study, patients are selected based on clinical remission criteria and are not screened with US. Consequently, there may be a higher likelihood of including patients with urate deposits at baseline, who are therefore at greater risk of flares compared to those in STING [22]. Predicting flares is one of the main secondary objectives of the GO TEST Finale.

Interestingly, both RCTs provide a unique opportunity for translational research into the effects of rising SUA on various inflammatory parameters, particularly the activation of the innate immune system. It has been demonstrated that hyperuricemia and gout flares can induce epigenetic changes and the adaptation of the innate immune system, contributing to a heightened pro-inflammatory state [25,26]. It is hypothesised that long-term normo-uricemic states and the absence of gout flares under ULT treatment will reset this pro-inflammatory state.

After ULT discontinuation, this pro-inflammatory state might reemerge in a subset of patients. We anticipate identifying immunological, metabolomic, and (epi)genetic changes that could predict this functional reprogramming and subsequent gout flares. These changes are expected to vary between individuals and may be influenced by the rise in SUA, duration of gout disease, duration of prior ULT treatment and remission, as well as comedications and comorbidities. Such findings could form the basis for a personalised ULT discontinuation strategy for gout patients.

In conclusion, both the GO TEST Finale and the STING trials address the same critical question: "once the SUA target is reached and gout symptoms have resolved, should patients continue lifelong ULT treatment?" The differences in study designs and patient profiles will hopefully lead to complementary findings, contributing to a resolution of this aspect of gout treatment.

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