Treating to target: a strategy to cure gout

Fernando Perez-Ruiz

Acute gout attacks and the long-term complications of gout are associated with the deposition of monosodium urate (MSU) monohydrate crystals in the joints and soft tissues, causing acute and chronic inflammation. The aim of long-term treatment is to reduce the serum urate (sUA) level to 6 mg/dl (<360 μmol/l), below the saturation point of MSU, so that new crystals cannot form and existing crystals are dissolved. Serial joint aspiration studies confirmed the disappearance of crystals with effective urate-lowering therapy. There is good evidence that achieving sUA <6 mg/dl (360 μmol/l) results in freedom from acute gout attacks, and shrinkage and eventual disappearance of tophi. Gout patients must be informed about their diagnosis and educated about gout management including the importance of compliance with long-term treatment. Patients starting urate-lowering therapy need to understand the importance of prophylactic therapy with colchicine or NSAIDs to reduce the risk of ‘mobilization flares’ in the first few months. In the long term, reduction in the sUA below the target level will result in gout being effectively cured.

KEY WORDS: Gout, Monosodium urate, Urate-lowering, Treatment target, Arthrocentesis, Crystals, Tophi, Cure.

Introduction

As already discussed in the first paper in this supplement [1], gout is one of the most common inflammatory arthritic diseases. It is a true crystal deposition disease and both acute episodes of inflammation (the so-called gout flares or attacks) and the long-term sequelae due to chronic inflammation of gout are induced by monosodium urate (MSU) monohydrate crystals formed in the tissues. If there are no MSU crystals present, gout cannot occur. This means that if the tissue environment urate concentration is reduced sufficiently, existing crystals are dissolved and new crystals can no longer form, which essentially cures gout. This potential for cure with adequate long-term treatment makes gout a rewarding condition for clinicians to manage. This paper will discuss the role of MSU crystals in the pathogenesis of acute and chronic gout and the importance of targeting a low serum urate (sUA) level during the treatment of chronic gout, in order to achieve the clinical benefits of freedom from acute gout attacks, resolution of tophi and prevention of structural damage to joints and tissues. Practical aspects of the long-term management of gout patients are also reviewed.

Hyperuricaemia as the underlying cause

It is clear that long-standing hyperuricaemia is the principal factor in the occurrence of gout, based not only on the epidemiological evidence, but also on physicochemical principles. Uric acid is a weak acid that is present in plasma as MSU. Numerous studies have shown that the solubility of MSU is strongly temperature dependent and that the saturation threshold at 37°C is ~6.8 mg/dl (408 μmol/l) [2]. However, only a small proportion of patients with hyperuricaemia develop gout and hence other factors must determine whether crystal formation occurs. Several groups have shown that SF from gout patients with hyperuricaemia develop gout and hence other factors must determine whether crystal formation occurs. Several groups have shown that SF from gout patients enhances the formation of MSU crystals [3, 4]. In one study, the addition of SF from gout patients to super-saturated solutions of sodium urate under physiological conditions greatly enhanced crystal formation, whereas SF from OA patients had a modest effect and fluid from RA patients had little effect [3].

Crystals are present, and may be retrieved by aspirating the SF of gout patients during gout flares, but also during asymptomatic (intercritical) periods [5]. However, no correlation has been observed between the size, shape and numbers of crystals in the SF and the severity of inflammation—some patients with severe acute gout may have only a few crystals. Hence, other factors must affect the severity of the inflammatory response in gout [6].

Formation of crystals may initially start in the joint cartilage in an orderly way, suggesting epitaxial nucleation and growth [7].

Acute gout flares

Deposition of crystals may continue for months or years without causing symptoms [8], until shedding of crystals into the SF triggers the first episode of acute gout. Innate immunity (through toll-like receptors) may be involved in MSU-induced macrophage activation [9]. MSU crystals are intensely inflammatory and recent research has provided new insights into the inflammatory process. MSU crystals are phagocytosed by monocytes and macrophages, activating the NALP3 inflammasome and triggering the release of IL-1 and other cytokines. This leads to infiltration of neutrophils and the symptoms of an acute flare [10–12].

Acute gout attacks typically resolve spontaneously and differentiated macrophages, through secretion of TGF-β, may exert a protective role to the joint [13].

Chronic gout

Long-standing persistence of MSU crystals may also cause chronic neutrophilic inflammation [14], osteoclast activation [15] and chronic granulomatous infiltration of the synovium (Fig. 1). Micro-aggregates of MSU crystals occur in all patients with gout, but in some, macroscopic aggregates occur, manifested as tophus formation.

Tophi are usually considered to be a late manifestation of gout. However, intra-articular tophi have been reported before an acute gout attack has occurred [16]. Recent imaging studies have highlighted the presence of asymptomatic tophi not apparent on physical examination [17]. In a recent ultrasound study of patients with asymptomatic hyperuricaemia, tophi were detected in the tendons, synovial membrane or soft tissues in 12 of the 35 examined (34%). Power Doppler showed evidence of inflammation in two-thirds of these [8]. As well as diagnosing tophi, ultrasound can also be useful to detect the deposition of urate crystals on the articular cartilage [18]. MRI and CT are also valuable for detecting asymptomatic tophi [17].
Target sUA in chronic gout

Since it is clear that gout is the consequence of the accumulation of uric acid in the body, the logical way to treat the condition is to lower the sUA level and deplete the body urate pool. The clinical manifestations of gout are due to deposition of MSU crystals and if the crystals are dissolved completely and no new crystals can form, then the condition is cured. To achieve this, the sUA (and hence the tissue and joint uric acid levels) must be reduced below the saturation point of MSU under physiological conditions.

This has been recognized in recent evidence-based recommendations from the European League against Rheumatism (EULAR) Task Force for Gout, which recommend that the sUA should be reduced to a target of \( \leq 6 \text{ mg/dl} \) \((360 \mu\text{mol/l})\) [19]. The authors of the recommendations point out that the target sUA level should be linked to the saturation level of MSU rather than to the normal laboratory range, which can vary between populations and with time. It is also acknowledged in the guidelines that the target sUA may vary depending on the characteristics of the patient and a lower target may be appropriate in patients with extensive crystal deposition. The British Society of Rheumatology (BSR) has also published guidelines for the management of gout and these recommend a stricter sUA target of \(< 5 \text{ mg/dl} \) \((< 300 \mu\text{mol/l})\) [20].

Outcome measures

The aim of treatment is to dissolve the crystals, leading to freedom from acute attacks of gout, reduction and disappearance of tophi and prevention of further tissue damage [21]. In the study by Pascaul and Sivera [22], arthrocentesis was performed in 18 patients before the initiation of urate-lowering therapy with benzbromarone or allopurinol plus benzbromarone, which are highly effective treatments. The process was repeated every 3 months and it was found that crystals soon disappeared from the SF after the dramatic reduction in sUA (Fig. 2) [22]. The median sUA fell from 9.2 mg/dl \((550 \mu\text{mol/l})\) before the start of treatment to 4.8 mg/dl \((290 \mu\text{mol/l})\) after 3 months of treatment. The time required for the disappearance of urate crystals ranged...
from 3 to 33 months and was correlated with the duration of gout ($r = 0.71, P < 0.01$).

Studies have consistently shown a relationship between sUA levels and the risk of gout flares, providing compelling evidence for targeting low sUA levels. In a retrospective study of 267 patients, 87% of whom received urate-lowering therapy, there was a strong correlation between the average sUA level and the recurrence of gout attacks: logistic regression analysis showed that the lower the sUA, the less likely the patient was to experience an acute attack ($P < 0.001$). The mean sUA in treated patients who experienced gout attacks ($n = 69$) was 7.01 mg/dl (420 $\mu$mol/l) compared with 6.36 mg/dl (388 $\mu$mol/l) in those who were free of attacks ($n = 163$) [23]. In another study, patients with sUA >6 mg/dl (>360 $\mu$mol/l) experienced a mean of six attacks of gout in the previous year and MSU crystals were present in 14 of 16 patients on joint aspiration. In contrast, the group with sUA levels $\leq$6 mg/dl ($\leq$360 $\mu$mol/l) for at least 12 months experienced a mean of one attack in the previous year and almost half had not experienced an attack for 2 years [24]. These findings were confirmed in a prospective study in 36 patients, which showed that gout flares were almost completely eliminated by the second year of urate-lowering therapy targeting the reduction of sUA $<6$ mg/dl (360 $\mu$mol/l). The mean number of flares was 3.4 ($\pm$1.62) per patient-year in the year before the initiation of therapy, 0.93 ($\pm$1.16) in the first year and 0.06 ($\pm$0.25) in the second year of treatment [25].

Maintaining the sUA level at $<6$ mg/dl (360 $\mu$mol/l) also results in a reduction in tophus size. In 14 patients with a gout diagnosis confirmed by the presence of crystals, who underwent ultrasound examination before and after 12 months of urate-lowering therapy, there was an inverse correlation between the mean reduction in the maximal tophus diameter and the average sUA level. There was a similar inverse correlation between change in tophus volume and sUA levels (Fig. 3) [26]. These results are in contrast with old studies suggesting that sUA levels did not have an impact on the progression of gout [27]; but a careful review of the results shows that sUA levels in these series were not targeted to $<6$ mg/dl (360 $\mu$mol/l), and most patients did not show ‘subsaturating’ urate levels [27]. Furthermore, the only patient who experienced disappearance of tophi showed sUA levels $<4$ mg/dl [27].

Some evidence also suggests that the lower the sUA level, the faster the decrease in tophus size, implying that a lower sUA target might be appropriate in patients with severe tophaceous gout [26, 28]. In another study in 63 patients with crystal-proven gout, there was a linear correlation between the sUA level and the speed of reduction of tophus size (Fig. 4) [28]. This supports the previously suggested concept that existing crystal deposits will be dissolved more quickly at lower sUA levels [29]. In these studies [26, 28], the combination of allopurinol and sulphinpyrazone or allopurinol and benzbromarone resulted in a striking reduction of subcutaneous tophi. Although not uncommon in the clinical practice of those with a special interest in gout [22, 28], there is no controlled study or long-term follow-up on how to manage combination therapy. Due to the present restrictions in benzbromarone prescription in the European Union due to liver toxicity concerns, the practical approach would be to consider combination therapy in patients in whom other urate-lowering drugs have not achieved the sUA target for the treatment of gout.

**Practical issues in the management of gout patients**

It is important that the patients are informed about their diagnosis and educated about gout. It is particularly important to help them understand that MSU crystal observation equals the certainty of the diagnosis and that there is a need for adequate, long-term therapy designed to eradicate the crystals. It is also essential to explain to the patient about the role of lifestyle changes and non-pharmacological approaches to the management of gout. Obese patients should lose weight gradually and the diet should be adjusted to avoid an excess intake of proteins from meat and fish (but not proteins of dairy origin) and other high-purine foods. The intake of alcohol, especially beer, should be reduced to a minimum [19, 20]. While these measures may have a relatively modest effect on the sUA level, they are quite beneficial for the general health of the patient.
Hyperuricaemia is often associated with dyslipidaemia, hypertension, insulin resistance and obesity as part of the metabolic syndrome [30] and hence management of these risk factors should be considered as part of the overall therapeutic approach to gout.

There is no consensus on when to start therapy with urate-lowering drugs. All experts would agree that patients with severe gout (recurrent flares, polyarticular joint involvement, presence of tophi or structural joint involvement) should be encouraged to start a urate-lowering drug. The issue is whether waiting for severe gout to develop should be considered as good clinical practice. Reference to some studies may help patients and doctors in their decision-making process. Over 50% of the patients not treated with urate-lowering drugs developed tophaceous X-ray involvement, suggesting that untreated gout is not a mild, non-progressive disease [31]. Severity of gout is also associated with a higher rate of ischaemic heart disease [32], and gout itself, independent from hyperuricaemia and other well-known vascular risk factors, may be associated with an increased risk of myocardial infarction [33]. Furthermore, in a hypothetical decision model analysis, urate-lowering therapy would be cost saving for patients with two or more flares a year, and for patients with one flare a year and at risk of developing adverse events to NSAIDs [34].

With this in mind, patients and doctors should consider carefully the advantages (high rate of success in preventing both flares and the development of severe gout) and the risks (low rate of adverse events due to urate-lowering drugs) when making their decisions.

Once a decision has been taken to start urate-lowering therapy, especially if urate-lowering drugs are needed, it is important that the patient understands that there is a risk of ‘mobilization flares’ in the first few months of treatment. Such flares are thought to be caused by the rapid reduction in sUA after the start of urate-lowering agents or after a change in dose. Acute attacks occur after the initiation of all urate-lowering treatments and it is noteworthy that a high incidence has been observed with pegloticase, which causes a very rapid and dramatic fall in sUA [35].

The EULAR recommendations include initiating urate-lowering drugs at low dose, with step-up increase of dose, if tolerated, to properly control sUA levels [19]. Rapid reduction of sUA to subtherapeutic levels has been associated with an increase in the risk of gout flares [36–38], so reduction of sUA levels should be as slow as possible [36]. Initiating prophylactic therapy with either low-dose colchicine or an NSAID during the first months of urate-lowering therapy to reduce the risk of acute flares has also been recommended [19]. There have been two randomized controlled trials, published three decades apart, that evaluate the use of colchicine in this way [39, 40]. In one study, in patients being treated with probenecid, the addition of colchicine 1.5 mg/day (0.5 mg three times daily) resulted in a significant reduction in the number of acute attacks in the 6-month period (P < 0.05) [39]. In the second trial, prophylaxis with colchicine at a dose of 0.6 mg twice daily for 6 months during the initiation of allopurinol, significantly reduced the frequency and severity of acute flares (P = 0.008) [40]. The evidence to support the use of NSAIDs is less robust (no trial data available) but these agents are used as an alternative. In all cases, the balance of risks and benefits must be considered [19, 20].

It should be explained to patients that mobilization flares, if they occur, can be regarded as the ‘price to pay’ for the cure of gout and that in any case the risk can be reduced with prophylactic therapy. The patient also needs to understand about the importance of adhering to the prescribed therapy in order to achieve the sUA target and maintain sUA levels in the long term to finally eradicate MSU crystals. It is important to monitor sUA levels regularly to ensure that the target is met and also to check on compliance.

As discussed above, long-term urate-lowering therapy to achieve sUA levels ≤6 mg/dl (360 μmol/l) results in almost complete prevention of acute gout flares. It is normally recommended that urate-lowering therapy should be continued indefinitely. However, it is reasonable to ask whether it is possible to withdraw urate-lowering therapy after a long period of sustained control of the sUA, resulting in depletion of the body pool of uric acid. To answer this question, a prospective observational study was undertaken in patients who had received ≥5 years of urate-lowering therapy [41]. Patients were followed up for up to 6 years after withdrawal of urate-lowering therapy and sUA levels were measured regularly during this time. Patients were stratified according to the median sUA during urate-lowering therapy; the group with mean sUA levels of <5.05 mg/dl (<303 μmol/l) during therapy had a mean period of 49 months without recurrence compared with 34 months in those with higher sUA levels (Fig. 5). Similarly, those with mean sUA levels <8.75 mg/dl (<525 μmol/l) after withdrawal of urate-lowering therapy had a mean period of 47 months without recurrence compared with 34 months in those with higher sUA levels after urate-lowering therapy withdrawal. This suggests that, following a prolonged period of good control of sUA levels, it may be feasible to withdraw treatment for a period, or at least the sUA control target may be less rigid during the long-term (‘crystal formation prevention’) period of treatment than during the initial (‘crystal depleting’) period of treatment.

Management of patients with comorbidities

It is important to consider comorbidities in gout patients [42]. Renal function impairment function should be assessed by estimating creatinine clearance [43] rather than relying on the serum creatinine level. In patients with renal impairment, the dose of allopurinol must be adjusted according to renal function [44], and some uricosuric drugs may not be effective—such as probenecid and sulphinpyrazone—in patients with moderate renal function impairment, although benzbromarone may still show efficacy, although only at higher doses, in patients with moderate renal function impairment [25]. Severe allopurinol toxicity has been associated with renal function impairment due to the accumulation of oxyipurinol, its active metabolite, which is renally excreted [45], and not to a direct toxic effect on the kidneys. Although genetic predisposition has been recently reported in 100% of the Han Chinese showing Severe Cutaneous Adverse Reactions (SCAR) to allopurinol [46] and in 55% of the patients of European ancestry [47], renal function impairment was the other, highly statistically significant, factor associated with SCAR in patients on allopurinol [46]. In addition, the side effects

![Figure 5](https://academic.oup.com/rheumatology/article-abstract/48/suppl_2/ii9/1773536/1773536)
of colchicine and NSAIDs may be more frequent in patients with renal dysfunction and prescription use should be restricted in renally impaired persons to treat acute flares and for long-term prophylaxis [48].

Conclusions

In summary, gout is a crystal deposition disease that is associated with acute and chronic inflammation. However, it can be cured by long-term reduction in the sUA level <6 mg/dl (360 μmol/l), sufficient to dissolve crystal deposits and prevent formation of new crystals. This results in freedom from acute gout attacks, shrinkage and eventual disappearance of tophi and prevention of further tissue damage. While gout itself can be cured by lowering the sUA level below this target, joint and tissue damage that has already occurred may not be reversible, emphasizing the importance of treating the condition before such permanent damage has occurred.

In the author’s personal opinion, for all patients except those with very mild gout, the lower the sUA level the better during the first few years of treatment. However, a level close to the saturation level may be acceptable later on, once the body urate pool has returned to normal and crystal deposition cleared.

Finally, it is important to educate the patient about their disease and the importance of their contribution to (compliance with) long-term treatment.

Rheumatology key messages

- The acute and chronic manifestations of gout are caused by MSU crystals.
- ‘No crystals, no further gout’, but sequelae may persist.
- Gout can be cured by reducing sUA levels <6 mg/dl, which dissolves crystals.

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