Reassessing serum urate targets in the management of refractory gout: Can you go too low?

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Abstract

Purpose of review—Growing awareness of patients with refractory gout is prompting a reassessment of treatment strategy. This article reviews the current practice of targeting serum urate concentrations (sUA) in the mid-normal range (roughly 4–6 mg/dL), and considers the rationale for more aggressively lowering sUA in patients with poorly controlled chronic gout. Some hypothetical concerns with inducing hypouricemia are considered, and relevant clinical evidence is evaluated.

Recent findings—Recent studies confirm the benefits of modestly reducing sUA in many gout patients. However, tophi and tissue stores of monosodium urate crystals resolve slowly, particularly in patients with longstanding disease. Consistent with physicochemical principles, the rate of decrease in tophus size increases with a reduction in sUA concentration over a broad range. Reducing sUA to near or below 2 mg/dL can be achieved in some patients with current urate lowering drugs, but new drugs now under investigation may be more effective. As a free radical scavenger, uric acid has been postulated to protect from oxidative stress. However, inherited disorders associated with profound, lifelong hypouricemia indicate that maintaining sUA near or below 2 mg/dL would probably be safe.

Summary—Targeting low sUA could improve the elimination of tissue urate stores and achieve better control of disease in patients with refractory gout.

Keywords
Gout; tophus; hypouricemia; pegloticase; febuxostat

Introduction

A 1987 letter to the British Medical Journal offered advice on the proper dosing of allopurinol, noting that its use over the previous two decades “had caused severe tophaceous gout to all but vanish” [1]. Two decades later, the prevalence of gout is increasing and tophaceous gout has “re-emerged”. Several factors have contributed to this discouraging trend, including the continuing wide variation in the way urate-lowering therapy (ULT) is applied by physicians, and adhered to by patients; additionally, ULT is poorly tolerated or ineffective in a subset of patients with “refractory” or “treatment failure” gout [2–8].

New drugs tested in recent clinical trials may have a greater urate-lowering capacity than those available during the past 40 years [9]. If they are to be used successfully, it may be necessary to re-assess treatment strategy. I will review current views on serum uric acid
concentration (sUA) targets for ULT, and consider the potential benefits and risks of more aggressively lowering sUA, particularly in severely affected patients.

**Serum Urate Targets – Conventional and unconventional approaches**

**Conventional strategy – one target for all patients**

The role of ULT in gout management is to prevent the formation and deposition of monosodium urate (MSU) crystals. Minimally, this requires maintaining the concentration of urate below the limit of solubility in plasma and extracellular fluid, which is approximately 0.42 mM (7 mg/dL). Frequently cited sUA targets are ≤ 6 mg/dL (0.36 mM) or ≤ 5 mg/dL (0.30 mM) [10–13]. Clinical studies of varying size and design have shown that regardless of the ULT regimen used, achieving these targets is associated with benefit. For example, some relatively recent studies employing allopurinol and uricosuric agents, alone or in combination, have documented a reduction in the incidence of gout flares [14,15], elimination of MSU crystals from synovial fluid [14,16*], and reduction in tophus size [17,18]. A target sUA of <6 mg/dL has been incorporated into EULAR guidelines for gout therapy [13], and was used as the primary endpoint in recent clinical trials of febuxostat, a non-purine xanthine oxidase inhibitor, and pegloticase, a pegylated recombinant mammalian urate oxidase [18,19].

Although there is general agreement that targeting sUA levels of ≤6 or ≤5 mg/dL is meaningful, there has been little attention given to a lower limit, or target, for ULT [20*]. This should not be surprising: rheumatologists caring for patients referred with chronic gout are more concerned with just achieving the “≤6 mg/dL” target, than with being “too successful”. Once that target is reached, efforts to further reduce sUA are not pursued. However, it is useful to note that, at least in gout clinical trials, sUA levels well below 6 mg/dL have been achieved with conventional ULT (i.e. xanthine oxidase inhibitors and uricosuric agents) in a significant proportion of subjects. For example, in a recent trial in patients with relatively preserved renal function, mean sUA achieved with the potent uricosuric agent benzbromarone (no longer available in most countries) was 0.19 ± 0.07 mM (3.2 ± 1.2 mg/dL) [12]. In the 52 week long phase 3 trial of febuxostat, 41% of patients who received 120 mg/day had sUA of “<4 mg/dL” at their final visit [18].

**Individualized sUA targeting**

A recent review argued that it was appropriate to individualize sUA targets: ≤6 mg/dL for most patients, particularly those with a relatively recent onset of gout; but for patients with severe disease, “reducing sUA levels as far as possible with ULT, as long as it is still tolerated, can be considered” [20*]. It was to pursue such a strategy that, in 1993, led me to initiate a project to develop a pegylated mammalian uricase (now pegloticase) as an “orphan drug” for treating severely affected gout patients who were refractory to conventional ULT [21]. In phase I trials we demonstrated the ability of PEG-uricase to rapidly reduce sUA to <2 mg/dL in patients with refractory gout [22,23]. In a recently reported phase 2 trial in patients with “treatment failure gout”, 8 mg of pegloticase infused every 4 weeks or every 2 weeks lowered mean plasma UA to 3.2 mg/dL and 1.4 mg/dL, respectively, averaged over the 4-month long period of observation [19].

To date, no clinical trial has evaluated the consequences, good or ill, of reducing sUA to levels below 2 mg/dL (0.12 mM), which is usually considered “hypouricemia”[1]. I will

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1Hyperuricemia is defined both by the solubility of sodium urate, a physicochemical property, and by the distribution of sUA values in a particular demographic population, e.g. as 2 SD above the mean. Hypouricemia is defined solely by the population distribution of sUA levels.
discuss below what seem to me to be the main pros and potential cons of doing so in severely affected patients with chronic gout.

**The rationale for “Going Low”: speed the resolution of MSU deposits**

In patients with chronic gout, eliminating MSU deposits in tissues is essential for controlling, and some believe curing [5,20*] the disease. In practice, monitoring the depletion of tissue MSU stores after initiating ULT is not easily accomplished [14]. However, two recent clinical studies in which this was attempted indicate that the rate at which MSU deposits resolve is slow, and is a function of both disease duration and the degree of sUA reduction achieved.

In one study of 18 patients with non-tophaceous gout, sUA declined to 2.7–5.4 mg/dL (0.16–0.32 mM) in all subjects within 3 months of starting ULT [16*]. However, it took 12 months with normalized sUA for MSU crystals to disappear from asymptomatic knee or first MTP joints in patients who had gout for <10 years, vs. 18 months in those with gout for more than 10 years. In a second study of 63 patients with tophaceous gout, the size of a single tophus was monitored during 5 years of treatment with allopurinol, benzbromarone, or the two drugs combined [17]. Complete tophus resolution took an average of ~20 months with combined therapy, which reduced mean sUA to ~4 mg/dL, vs. ~29 months with allopurinol alone, which reduced mean sUA to ~5.4 mg/dL. In individual patients, mean sUA (averaged over the entire treatment period) ranged from about 7 to as low as 2.5 mg/dL; there was a linear, inverse relationship between mean sUA and the rate of decrease in tophus size.

The observed dependence of the rate of tophus resolution on sUA concentration is consistent with physicochemical principles [24], and with in vitro experiments showing that the rate at which MSU crystals dissolve is proportional to the degree of urate undersaturation in the surrounding fluid [25]. This relationship provides a compelling rationale for targeting sUA as low as can be achieved with safety, in order to ensure timely, effective elimination of MSU deposits in patients with longstanding gout.

**Are there significant negative health consequences of very low sUA?**

Initiating ULT can trigger a transient increase in gout flares [15,18,26]. These flares might be more frequent when sUA levels are lowered to well below present targets, although this has not been examined in a clinical trial. However, the issue addressed here is whether the risk of acquiring some serious illness other than gout might increase if hypouricemia is maintained by ULT (and whether that risk is larger than if sUA were maintained within the normouricemic range, e.g. <6 but >2 mg/dL). Textbook chapters on gout caution against inappropriate use or excessive dosing of ULT, but the concern is with the risk of drug side effects and hypersensitivity, rather than any known dangers of iatrogenic hypouricemia. Indeed, there has been far more investigation into the medical consequences of hyper- than hypo-uricemia (a Pubmed search for “hyperuricemia” yielded 3619 citations, vs. 326 for “hypouricemia”).

**Hypouricemia and oxidative stress**

A hypothetical concern with inducing hypouricemia stems from the “Ames hypothesis” - that urate is a physiologically important free radical scavenger, which protects humans from a growing list of diseases in which oxidative damage has been implicated [27]. A specific claim, which has received much attention, is that urate protects from neurodegenerative disorders, including Multiple Sclerosis and Parkinson’s disease, by preventing damage to CNS myelin caused by the powerful oxidant peroxynitrite [28-30*,31]. This concern is
based on epidemiologic studies showing that sUA levels are modestly lower in affected patients than in controls. For example, among 18,000 males in the Health Professionals Follow-up cohort, mean plasma UA (single measurement) in 84 incident cases of Parkinson’s disease was 5.7 mg/dL, vs. 6.1 mg/dL in 165 matched controls; men in the top quartile of plasma UA had a 55 percent lower rate of Parkinson’s disease than men in the bottom quartile [30*].

These and other similar reports impute significant risk of neurodegenerative diseases to “low” sUA levels that are well within the normal range, and often achieved in gout patients receiving ULT. A full critique of the “urate is neuroprotective” hypothesis is beyond the scope of this article, but some observations suggest that it is too simplistic, including 1) Urate levels in brain (presumably where CNS protection occurs) are far lower than in plasma. CSF urate concentrations in Parkinson’s disease patients and controls differed by <10%, and were <2% of urate levels in plasma in each group [32]. 2) Putatively “neuroprotective” sUA levels in the high normal range have been associated with mild cognitive impairment and ischemic pathology in older individuals [33*]. 3) Chemical reactions involving urate and free radicals are extremely complex, and can result in pro- as well as anti-oxidant activity [28,34].

Oxidative stress has also been implicated in many aspects of cardiovascular disease, but the associations in that area are with high sUA (as reviewed by Dr. Edwards elsewhere in this issue). For example, high normal sUA has been associated with hypertension in adolescents, and blood pressure declined during treatment with allopurinol [35**]. In two recent large epidemiologic studies the highest quartiles or quintiles for sUA levels were associated with an increased risk, relative to the lowest sUA levels, of cardiovascular disease associated mortality [36*,37*]. These findings do not suggest any obvious danger in markedly lowering sUA in patients with chronic gout who also have cardiovascular disease. Whether eliminating stores inflammatory MSU crystals might have benefit, beyond achieving control of their gout, is unknown.

The health impact of hypouricemia – lessons from experiments of nature

Perhaps most relevant to the question of the safety of ULT-induced hypouricemia are two rare inherited disorders that result in lifelong hypouricemia, with sUA concentrations constantly <1mg/dL. Individuals with xanthinuria lack functional xanthine oxidase and therefore cannot produce uric acid [38], whereas individuals with the condition known as renal hypouricemia lack a functional URAT1 urate-anion exchange protein, and are unable to reabsorb uric acid from renal tubules [39]. Each of these disorders is associated with renal stones, composed of xanthine in xanthine oxidase deficiency, and uric acid in URAT1 deficiency. Some patients with xanthinuria also have a myopathy, possibly related to xanthine deposits in muscle, and some patients with renal hypouricemia have occasionally developed transient renal failure after strenuous exercise, possibly due to a sudden increase in urate production and excretion. However, many, if not most, equally hypouricemic individuals with each of these disorders are healthy, with an apparently normal lifespan. The full natural history of these rare conditions may not be known. But available information does not raise flags regarding the safety of even profound hypouricemia.

Implementation

As noted, sUA levels approaching hypouricemia can be achieved with current ULT in some gout patients; in others combining a xanthine oxidase inhibitor and a uricosuric might be required. A relatively small recent study found that lower sUA levels could be achieved without an increase in adverse events when the dose of allopurinol was increased from 300
to 600 mg/day, at least in patients with relatively good renal function who were treated for only a few months [40]. Febuxostat might provide an alternative to allopurinol dose escalation, although that comparison has not yet been evaluated in a clinical trial. However, renal insufficiency is not uncommon in patients with longstanding gout, and could both reduce the response to uricosurics and diminish the ability to excrete soluble urate mobilized from MSU deposits when xanthine oxidase is inhibited. The uricolytic action of pegloticase is independent of renal function. Phase 3 clinical trials of intravenous pegloticase, and a longer open-label extension, have recently been concluded. When available, the results of those trials should be informative in gauging the risks and benefit of maintaining hypouricemia in patients with chronic gout and its associated comorbidities.

**Conclusion**

Clinical trials will be needed to refine strategies and proper indications for markedly lowering sUA, and to assess safety and efficacy. However, theoretical reasons and some clinical evidence suggest that maintaining very low sUA will significantly speed the elimination of tophi and tissue MSU deposits in patients with chronic gout, which should lead to better control, and even cure, of their disease. Although uric acid is postulated to play a role in protecting from oxidative stress, “experiments of nature” indicate that maintaining sUA near or below 2 mg/dL would probably be safe. In my opinion, the potential benefit to patients with refractory gout would justify taking hypothetical risks. Future trials might be designed to determine whether a finite period of sustained, pharmacologically induced hypouricemia might result in prolonged freedom from gout attacks and reduced arthropathy, or might enhance the subsequent clinical response to less potent ULT.

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37*. Strasak AM, Kelleher CC, Brant LJ, Rapp K, Ruttmann E, Concin H, Diem G, Pfeiffer KP, Ulmer H. Serum uric acid is an independent predictor for all major forms of cardiovascular death in 28,613 elderly women: a prospective 21-year follow-up study. Int J Cardiol 2008;125:232–239. Both of these large epidemiologic studies confirm the association of cardiovascular risk with urate levels in the upper normal range. The lowest quartiles or quintiles of sUA concentration were associated with the lowest risk. These results are useful in gauging whether inducing low urate levels might be of risk to gout patients with cardiovascular disease. [PubMed: 18237790]


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