Published in final edited form as:
Curr Opin Rheumatol. 2009 March ; 21(2): 138–142. doi:10.1097/BOR.0b013e3283257b83.

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

Michael S. Hershfield, MD
Duke University Medical Center, Durham, NC 27710 USA

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

Proofs and correspondence should be sent to: Michael S. Hershfield, MD, Box 3049, 418 Sands Building, Duke University Medical Center, Durham, NC 27710, USA, Tel: 919-684-4184; Fax: 919-684-4168; msh@biochem.duke.edu.

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

[1]Hyperuricemia 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 "neuro-protective" 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.

Acknowledgments

Dr. Hershfield is an inventor named on patents for pegloticase; he and Duke University may benefit financially under the terms of a licensing agreement with Savient Pharmaceuticals, Inc. Dr. Hershfield has on occasion been paid for consulting with, and currently receives grant support from Savient Pharmaceuticals. Additional grant support is from the FDA Office of Orphan Products Development.

References

1. Cameron JS, Simmonds HA. Use and abuse of allopurinol. Br Med J (Clin Res Ed) 1987;294:1504–1505.
2. Fels E, Sundy JS. Refractory gout: what is it and what to do about it? Curr Opin Rheumatol 2008;20:198–202. [PubMed: 18349751]
3. Mikuls TR, Farrar JT, Bilker WB, Fernandes S, Saag KG. Suboptimal physician adherence to quality indicators for the management of gout and asymptomatic hyperuricaemia: results from the UK General Practice Research Database (GPRD). Rheumatology (Oxford) 2005;44:1038–1042. [PubMed: 15870145]
4. Neogi T, Hunter DJ, Chaisson CE, Allensworth-Davies D, Zhang Y. Frequency and predictors of inappropriate management of recurrent gout attacks in a longitudinal study. J Rheumatol 2006;33:104–109. [PubMed: 16267879]
5. Pascual E, Sivera F. Why is gout so poorly managed? Ann Rheum Dis 2007;66:1269–1270. [PubMed: 17881662]
6. Schlesinger N, Schumacher HR Jr. Gout: can management be improved? Curr Opin Rheumatol 2001;13:240–244. [PubMed: 11333356]
7. Singh JA, Hodges JS, Toscano JP, Asch SM. Quality of care for gout in the US needs improvement. Arthritis Rheum 2007;57:822–829. [PubMed: 17530682]
8. Riedel AA, Nelson M, Joseph-Ridge N, Wallace K, MacDonald P, Becker M. Compliance with allopurinol therapy among managed care enrollees with gout: a retrospective analysis of administrative claims. J Rheumatol 2004;31:1575–1581. [PubMed: 15290738]

9. Sundy JS, Hershfield MS. Uricase and other novel agents for the management of patients with treatment-failure gout. Curr Rheumatol Rep 2007;9:258–264. [PubMed: 17531181]
10. Jordan KM, Cameron JS, Snaith M, Zhang W, Doherty M, Seckl J, Hingorani A, Jaques R, Nuki G. British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of gout. Rheumatology (Oxford) 2007;46:1372–1374. [PubMed: 17522099]
11. Reinders MK, van Roon EN, Houtman PM, Brouwers JR, Jansen TL. Biochemical effectiveness of allopurinol and allopurinol-probenecid in previously benzbromarone-treated gout patients. Clin Rheumatol 2007;26:1459–1465. [PubMed: 17308859]
12. Reinders MK, van Roon EN, Jansen TL, Delsing J, Griep EN, Hoekstra M, van de Laar MA, Brouwers JR. Efficacy and tolerability of urate lowering drugs in gout: a randomised controlled trial of benzbromarone versus probenecid after failure of allopurinol. Ann Rheum Dis. 2008
13. Zhang W, Doherty M, Bardin T, Pascual E, Barskova V, Conaghan P, Gerster J, Jacobs J, Leeb B, Liote F, et al. EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2006;65:1312–1324. [PubMed: 16707532]
14. Li-Yu J, Clayburne G, Sieck M, Beutler A, Rull M, Eisner E, Schumacher HR Jr. Treatment of chronic gout. Can we determine when urate stores are depleted enough to prevent attacks of gout? J Rheumatol 2001;28:577–580. [PubMed: 11296962]
15. Shoji A, Yamanaka H, Kamatani N. A retrospective study of the relationship between serum urate level and recurrent attacks of gouty arthritis: evidence for reduction of recurrent gouty arthritis with antihyperuricemic therapy. Arthritis Rheum 2004;51:321–325. [PubMed: 15188314]
16*. Pascual E, Sivera F. Time required for disappearance of urate crystals from synovial fluid after successful hypouricaemic treatment relates to the duration of gout. Ann Rheum Dis 2007;66:1056–1058. The results of this relatively small study imply that the time required to resolve tissue MSU deposits reflects the burden of MSU that had accumulated prior to ULT. [PubMed: 17223663]
17. Perez-Ruiz F, Calabozo M, Pijoan JI, Herrero-Beites AM, Ruibal A. Effect of urate-lowering therapy on the velocity of size reduction of tophi in chronic gout. Arthritis Rheum 2002;47:356–360. [PubMed: 12209479]
18. Becker MA, Schumacher HR Jr, Wortmann RL, MacDonald PA, Eustace D, Palo WA, Streit J, Joseph-Ridge N. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. N Engl J Med 2005;353:2450–2461. [PubMed: 16339094]
19. Sundy JS, Becker MA, Baraf HSB, Barkuizen A, Moreland LW, Huang W, Waltrip RW, Maroli AN, Horowitz Z. Reduction of plasma urate levels following treatment with multiple doses of pegloticase (polyethylene glycol-conjugated uricase) in patients with treatment-failure gout. Arthritis Rheum 2008;58:2882–2891. [PubMed: 18759308]
20*. Perez-Ruiz F, Liote F. Lowering serum uric acid levels: what is the optimal target for improving clinical outcomes in gout? Arthritis Rheum 2007;57:1324–1328. A timely review and analysis of the literature related to targets for ULT. [PubMed: 17907217]
21. Hershfield, MS.; Sundy, JS. Urate Oxidase (Uricase). In: Wortmann, RL.; Schumacher, HR.; Becker, MA.; Ryan, LM., editors. Crystal-induced arthropathies. Taylor & Francis; 2006. p. 401-410.
22. Ganson NJ, Kelly SJ, Scarlett E, Sundy JS, Hershfield MS. Control of hyperuricemia in subjects with refractory gout, and induction of antibody against poly(ethylene glycol) (PEG), in a phase I trial of subcutaneous PEGylated urate oxidase. Arthritis Res Ther 2006;8:R12. [PubMed: 16356199]
23. Sundy JS, Ganson NJ, Kelly SJ, Scarlett E, Rehrig CD, Huang W, Hershfield MS. Pharmacokinetics and pharmacodynamics of intravenous PEGylated recombinant mammalian urate oxidase in patients with refractory gout. Arthritis Rheum 2007;56:1021–1028. [PubMed: 17328081]
24. Lasaga AC, Luttge A. Variation of crystal dissolution rate based on a dissolution stepwave model. Science 2001;291:2400–2404. [PubMed: 11264534]
25. Erwin CL, Nancollas GH. The crystallization and dissolution of sodium urate. Journal of Crystal Growth 1981;53:215–223.

26. Wortmann RL. Effective management of gout: an analogy. Am J Med 1998;105:513–514. [PubMed: 9870838]

27. Ames BN, Cathcart R, Schwiers E, Hochstein P. Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: a hypothesis. Proc Natl Acad Sci USA 1981;78:6858–6862. [PubMed: 6947260]

28. Pacher P, Beckman J, Liaudet L. Nitric oxide and peroxynitrite in health and disease. Physiol res 2007;87:315–424.

29. Rentzos M, Nikolaou C, Anagnostouli M, Rombos A, Tsakanikas K, Economou M, Dimitrakopoulos A, Karouli M, Vassilopoulos D. Serum uric acid and multiple sclerosis. Clin Neurol Neurosurg 2006;108:527–531. [PubMed: 16202511]

30*. Weisskopf MG, O'Reilly E, Chen H, Schwarzschild MA, Ascherio A. Plasma urate and risk of Parkinson's disease. Am J Epidemiol 2007;166:561–567. A prospective case-control study, which found that normal, but relatively low plasma urate levels preceded the onset of neurologic symptoms of Parkinson's disease. The authors review other evidence that uric acid is neuroprotective. [PubMed: 17584757]

31. Koch M, De Keyser J. Uric acid in multiple sclerosis. Neurol Res 2006;28:316–319. [PubMed: 16687059]

32. Tohgi H, Abe T, Takahashi S, Kikuchi T. The urate and xanthine concentrations in the cerebrospinal fluid in patients with vascular dementia of the Binswanger type, Alzheimer type dementia, and Parkinson's disease. J Neural Transm Park Dis Dement Sect 1993;6:119–126. [PubMed: 8117408]

33*. Schretlen DJ, Inscore AB, Vannorsdall TD, Kraut M, Pearlson GD, Gordon B, Jinnah HA. Serum uric acid and brain ischemia in normal elderly adults. Neurology 2007;69:1418–1423. A cross-sectional observational study, which demonstrates that high normal levels of sUA are associated with an increased burden of cerebral ischemic pathology in older adults. The authors discuss the seemingly contradictory properties of uric acid, being both a "neuroprotective" antioxidant and a risk factor for neurologic dysfunction. [PubMed: 17909154]

34. Santos CX, Anjos EI, Augusto O. Uric acid oxidation by peroxynitrite: multiple reactions, free radical formation, and amplification of lipid oxidation. Arch Biochem Biophys 1999;372:285–294. [PubMed: 10600166]

35**. Feig DI, Soletsky B, Johnson RJ. Effect of allopurinol on blood pressure of adolescents with newly diagnosed essential hypertension: a randomized trial. JAMA 2008;300:924–932. A randomized, double blind cross-over trial demonstrating that allopurinol treatment reduced blood pressure in children with essential hypertension and sUA >6 mg/dL. Although subject to a number of limitations, the study provides intriguing evidence in humans that elevated urate levels might play a causal role in early hypertension. [PubMed: 18728266]

36*. Ioachimescu AG, Brennan DM, Hoar BM, Hazen SL, Hoogwerf BJ. Serum uric acid is an independent predictor of all-cause mortality in patients at high risk of cardiovascular disease: a preventive cardiology information system (PreCIS) database cohort study. Arthritis Rheum 2008;58:623–630. [PubMed: 18240236]

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]

38. Raivio, KO.; Saksela, M.; Lapatto, R. Xanthine oxidoreductase - role in human pathophysiology and in hereditary xanthinuria. In: Scriver, CR.; Beaudet, AL.; Sly, WS.; Valle, D., editors. The Metabolic and Molecular Bases of Inherited Disease. 8. McGraw-Hill; 2001. p. 2639-2652.

39. Ichida K, Hosoyamada M, Hisatome I, Enomoto A, Hikita M, Endou H, Hosoya T. Clinical and molecular analysis of patients with renal hypouricemia in Japan-influence of URAT1 gene on urinary urate excretion. J Am Soc Nephrol 2004;15:164–173. [PubMed: 14694169]

40. Reinders MK, Haagsma C, Jansen TL, van Roon EN, Delsing J, van de Laar MA, Brouwers JR. A randomised controlled trial on the efficacy and tolerability with dose-escalation of allopurinol

300–600 mg/day versus benzbromarone 100–200 mg/day in patients with gout. Ann Rheum Dis. 2008