

A Critical Reappraisal of Allopurinol Dosing, Safety, and Efficacy for Hyperuricemia in Gout

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Allopurinol, the first-line drug for serum urate–lowering therapy in gout, is approved by the US Food and Drug Administration for a dose up to 800 mg/d and is available as a low-cost generic drug. However, the vast majority of allopurinol prescriptions are for doses ≤ 300 mg/d, which often fails to adequately treat hyperuricemia in gout. This situation has been promoted by longstanding, non–evidence-based guidelines for allopurinol use calibrated to renal function (and oxypurinol levels) and designed, without proof of efficacy, to avoid allopurinol hypersensitivity syndrome. Severe allopurinol hypersensitivity reactions are not necessarily dose-dependent and do not always correlate with serum oxypurinol levels. Limiting allopurinol dosing to ≤ 300 mg/d suboptimally controls hyperuricemia and fails to adequately prevent hypersensitivity reactions. However, the long-term safety of elevating allopurinol dosages in chronic kidney disease requires further study. The emergence of novel urate-lowering therapeutic options, such as febuxostat and uricase, makes timely this review of current allopurinol dosing guidelines, safety, and efficacy in gout hyperuricemia therapy, including patients with chronic kidney disease.

Introduction

The central abnormality in gout is chronic hyperuricemia, most often due to decreased renal uric acid excretion and promotion of articular deposition of monosodium urate crystals. Gout is increasing in prevalence and many subjects have refractory hyperuricemia [1,2•,3,4]. Many have failed allopurinol therapy due to drug intolerance and are unable to manifest an adequate therapeutic response to

uricosurics due to chronic kidney disease (CKD). Fortunately, new antihyperuricemic treatments are in clinical development [1,2•,3]. Two compounds have undergone pivotal phase 3 studies: the pegylated uricase, pegloticase [2•], and the nonpurine, backbone-based, xanthine oxidase inhibitor, febuxostat [5].

In 2008, febuxostat was approved by the European Medicines Agency (EMA) and an expert advisory panel to the National Institutes of Health (NIH) recommended febuxostat approval in November 2008. However, because febuxostat has potential side effects, including the potential to cause elevated liver function tests, continuing cardiovascular safety studies were recommended to the NIH by the expert advisory panel in November 2008. Treatment with infusions of uricase is expected to be costly and has issues with infusion reactions and safety that are not yet resolved [2•]. Moreover, uricase therapy, in our opinion, is a treatment strategy best reserved for limited-term, tophus-debulking therapy in a small subgroup of very carefully selected patients [1]. As such, safer, cost-effective ways of using established, generic, urate-lowering drugs, such as allopurinol, need to be refined, particularly in this era of challenging economics, with a careful eye on optimal patient outcomes.

Current Allopurinol Treatment Guidelines

Dosing guidelines for allopurinol are substantially divergent and none are evidence based. In particular, allopurinol dosing in patients with CKD lacks consensus. Allopurinol has been approved by the US Food and Drug Administration (FDA) for doses up to 800 mg/d in treatment of hyperuricemia in patients with gout [6], with guidelines from the British Society of Rheumatology advocating a maximum dose of 900 mg/d [7]. Dosing guidelines from the FDA and European League Against Rheumatism (EULAR) advocate upward titration, starting from the minimal effective dose of 100 to 200 mg/d, to decrease the frequency of acute gout flares. This is followed by increasing the dosage steadily by increments of 100 mg/d (at intervals of 1 week or 2–4 weeks as recommended by the FDA and EULAR, respectively) until a normal serum urate level (< 6 mg/dL) is achieved, but not exceeding the maximum recommended

dose of allopurinol to do so [4,6]. Allopurinol can cause gastrointestinal (GI) intolerance, such as nausea and diarrhea, that appear to be dose-dependent. To improve GI tolerance, it has been advocated to divide allopurinol into two equal doses for daily amounts exceeding a total of 300 mg [6,8], with standard practice being a single morning daily dose of allopurinol for patients receiving a total ≤ 300 mg/d. FDA dosing guidance indicates that 200 to 300 mg/d is typically sufficient for patients with mild gout, whereas an average allopurinol dose of 400 to 600 mg/d is the expected average dose to control moderately severe tophaceous disease [6]. FDA dosing guidelines for allopurinol with renal dysfunction are incomplete, however, as they unequivocally advocate initiation and maintenance dose reductions with CKD. These guidelines also recommend limiting the maximum allopurinol dose to 200 mg/d (creatinine clearance level [CrCl], 10–20) and to 100 mg/d (CrCl < 10), without specifying a scale for dosing allopurinol in moderate CKD [6].

Perez-Ruiz et al. [9] advocated dose titration of allopurinol up to 600 mg/d, based first on efficacy studies in which the mean daily dose of allopurinol required to normalize serum urate level in a small study group of gout patients was 372 mg [9]. Secondly, a dosing ratio of allopurinol was constructed, based on CrCl calculated by the Cockcroft-Gault equation normalized to body weight and optimized to a maximum dose of allopurinol of 600 mg/d with optimal renal function [8]. Applying this ratio to a retrospective analysis of patients treated with allopurinol, about 40% fewer significant allopurinol toxicities were seen in patients receiving less than 400 mg of allopurinol per dL/d CrCl, and the only severe toxicities were seen with more than 600 mg of allopurinol per dL/d CrCl [8]. Despite the astute approach, the study format was not sufficiently robust to establish an evidence basis for this strategy [8].

The nephrology-based allopurinol maintenance dosing guidelines of Hande et al. [10] advocated a sliding scale of allopurinol doses, ranging up to a maximum of 400 mg/d for CrCl level of 140. These specific guidelines were designed for calibration to serum oxypurinol levels (and, theoretically, to thereby avoid allopurinol hypersensitivity syndrome [AHS]). They appear to be the most commonly adhered to recommendations in the United States and other countries where the vast majority of allopurinol prescriptions are for 300 mg/d or less [11].

Rash, typically maculopapular and associated with pruritus, develops in about 2% of patients treated with allopurinol, and in about 20% of patients treated with allopurinol and ampicillin or amoxicillin. Allopurinol-induced pruritus or skin rash in the absence of ampicillin or amoxicillin warrants immediate discontinuation of allopurinol. Oral allopurinol desensitization starting at low microgram daily levels of allopurinol, which only is successful in about 50% of subjects, is contraindicated with severe allopurinol cutaneous reactions in the clinical scenario in which uricosuric treatment is contraindicated.

Moreover, the process of compounding is cumbersome and time to reestablishment of effective allopurinol doses generally long. In some patients with minor cutaneous reaction in response to allopurinol doses higher than 300 mg/d, it is acceptable to attempt brief and carefully monitored simple challenges with a lower allopurinol dose, such as 100 mg/d, where uricosuric treatment is contraindicated. However, this strategy, as well as oral allopurinol desensitization, will not remain the best practice when other acceptable options that lower serum urate levels become available.

Direct nephrotoxicity of allopurinol occurs at high doses in rodents but is not a significant concern in humans. Bone marrow suppression is an uncommon side effect of allopurinol that seems dose-dependent. A death signal trend was linked to oxypurinol in a recent study of xanthine oxidase inhibition therapy of congestive heart failure [12], but other evidence has suggested beneficial effects of allopurinol treatment on blood pressure [13] and renal function [14]. Because so many patients with gout have metabolic syndrome, heavily consume alcohol, and take nonsteroidal anti-inflammatory drugs, altered liver function is common in allopurinol-treated patients. Increase in liver enzymes attributable to allopurinol can occur in up to 5% of subjects, most commonly as asymptomatic elevations of transaminases and alkaline phosphatase. Major allopurinol hepatotoxicity is rare. For example, none of the 1797 subjects receiving allopurinol developed fulminant hepatotoxicity in a recent review [15]. However, severe and even fatal allopurinol-associated hepatic disease does rarely occur [16–18]. Histology is variable in association with allopurinol-induced hepatotoxicity, with granulomatous hepatitis, cholestatic jaundice, and severe liver necrosis described in previous case reports. Moreover, allopurinol hepatotoxicity, typically reversible with drug discontinuation, is a feature of AHS. Taken together, the best practice recommendation is to regularly monitor the liver panel, chemistry profile, and hemogram differential in conjunction with serum urate level before and after allopurinol initiation, particularly in early treatment stages.

Allopurinol Hypersensitivity Syndrome: Clinical Manifestations and Risk Factors

Prevention of AHS, beyond being the primary driver of the guidelines by Hande et al. [10], remains a major concern among physicians. The incidence of AHS has been reported to range between 0.1% to 0.4% of treated patients (1–4 per thousand patients) [19,20]. Therefore, AHS is uncommon but not as rare as would be suspected in clinical practice. AHS may be limited to severe cutaneous reactions, such as toxic epidermal necrolysis or Stevens-Johnson Syndrome, or may feature variable combinations of eosinophilia, leukocytosis, fever, hepatitis, and renal involvement [10,19,21–23].

Table 1. Risk factors for allopurinol hypersensitivity syndrome

Definite
Recent onset (several months) of allopurinol therapy
HLA-B58 allele in subjects of Han Chinese and European ancestry
Chronic kidney disease
Suggested by some of the data at this point
Concomitant thiazide diuretic therapy
High allopurinol dose relative to renal function
Allopurinol use in patients with asymptomatic hyperuricemia

Mortality has been estimated to be up to nearly one quarter of AHS cases, with multiorgan system disease including hepatocellular changes and renal failure being a serious concern [10,19].

AHS pathophysiology remains unclear. Some have attributed AHS to direct toxic effects of accumulation of oxypurinol and dose-dependent hypersensitivity to oxypurinol [10]. AHS is likely driven by cell-mediated immunity to allopurinol and oxypurinol [24]. For example, in immunologic studies on a patient with AHS, Braden et al. [25] described T-cell infiltration in the liver, an increased peripheral blood CD8/CD4 ratio, and an oxypurinol-induced T-cell proliferative and activation response substantially greater than that to allopurinol [25]. More recently, the presence of HLA-B58 (and, in particular, the HLA-5801 allele in subjects of Han Chinese ancestry) has been identified as a major risk factor for severe allopurinol cutaneous reaction in both Han Chinese and European cohorts [21–23].

Critical Reappraisal of Allopurinol Dosing Guidelines for Hypersensitivity Syndrome Prevention in Chronic Kidney Disease

The guidelines of Hande et al. [10] for renal function–based adjustment of the allopurinol dose originated after literature review of case reports showing that most patients with AHS had renal insufficiency and received standard allopurinol doses (ie, 300 mg/d). Additional analyses correlated increased plasma levels of oxypurinol with decreasing renal function. It was therefore assumed that AHS was primarily linked to higher oxypurinol levels [10]. Although most cases developed AHS within 6 weeks of therapy, guidelines suggested maintenance dosing rather than initial starting doses of allopurinol [10]. Significant numbers of patients had hyperuricemia without gouty arthritis and many were on thiazide diuretics, which could be implicated via thiazide interference with the excretion of oxypurinol [10].

Current understanding of AHS risk factors is summarized in Table 1, and has been reviewed in detail elsewhere [26,27••,28]. Most importantly, the relationship between oxypurinol concentration and AHS

remains unproven, as it does with more minor cutaneous reactions [26,28]. No study has demonstrated that systematic dose reduction in renal disease attenuates AHS risk [26,27••]. In this context, many patients with AHS and CKD have been reported to develop AHS on renal function–adjusted doses of allopurinol [19,27••]. Hung et al. [21] observed no significant difference in dose between patients with allopurinol-induced severe cutaneous reactions compared with allopurinol-tolerant patients. Vazquez-Mellado et al. [28] conducted a retrospective study of gout patients on allopurinol longer than 1 month, and in all patients the initial dose was adjusted to CrCl. In groups that had the adjusted dose maintained or in which the dose was increased beyond renal function–based guidelines, only one patient developed AHS, and this individual had normal renal function and received 300 mg/d of allopurinol [28].

It has become clear that strict adherence to the Hande et al. [10] allopurinol maintenance dosing guidelines also leads to suboptimal hyperuricemia control [26,27••]. Higher levels of oxypurinol than those advocated by Hande et al. [10] are often required to achieve target serum urate with CKD [29]. Use of serum oxypurinol levels in this setting is more useful to rule out noncompliance as the cause of allopurinol treatment failure rather than to fine-tune allopurinol therapy [2•].

Current Allopurinol Dosing Guidelines With Respect to Attaining Benchmark Serum Urate Lowering

The most frequently employed benchmark for effective serum urate lowering is reduction to lower than 6 mg/dL, because urate becomes supersaturated in physiologic solutions at 6.7 to 7 mg/dL [30••]. It should first be noted that attaining serum urate levels lower than 6 mg/dL is desirable when attempting to debulk tophi in a timely way (ie, months) [2•]. Conversely, experienced practitioners are well aware that some patients can achieve improved, satisfactory control of gouty arthritis flares when serum urate is lowered to a stable level between 6 to 6.7 mg/dL. Settling for an aggressive benchmark is currently one manner in which dose-related allopurinol side effects may be avoided in some patients with CKD. Nevertheless, therapeutic achievement of serum urate less than 6 mg/dL has been associated with ultimately reduced frequency of acute gout flares, decreased tophus size, and decrease in detected urate crystals in synovial fluid, as recently reviewed [2•,30••]. In addition, it has been proposed that achievement of a serum urate level less than 6 mg/dL may also have beneficial effects on renal function [31,32]. However, it is not clear whether these effects are mediated by factors other than urate levels, such as antioxidant activity of allopurinol, possible urate-independent beneficial effects of allopurinol on hypertension, and changes in patterns of drugs used to treat gout, such as NSAIDs [13].

Dose titration of allopurinol more than 300 mg/d has been supported by Perez-Ruiz et al. [9] and by Reinders et al. [33••] in a recent randomized, controlled, open-label trial in gout patients (CrCl > 50). Specifically, in the first study phase, a patient subset received 300 mg/d of allopurinol, and in those in whom a serum urate level of approximately 5 mg/dL was not achieved at 2 months, the allopurinol dosage was increased to 300 mg twice daily in a second stage of the study [33••]. In the first study phase, only eight (26%) of 31 allopurinol-treated patients achieved a serum urate level lower than about 5 mg/dL, increasing to 21 (78%) of 27 patients with allopurinol dose doubling to 600 mg/d in the second phase, with only two patients stopping allopurinol due to adverse drug reactions [33••].

Three recent, large clinical trials comparing allopurinol with febuxostat provided large study numbers and further critical insight into allopurinol efficacy in the lowering of serum urate levels in gout patients [5,34,35]. Data from these studies indicate that 33% is a reasonable expectation for the relative amount of serum urate level lowering by allopurinol 300 mg/d in a population of gout patients with serum urate levels about 9.5 to 10 mg/dL, with about 25% to 30% with detectable tophi and renal function largely preserved [5].

Importantly, head-to-head comparisons of allopurinol and febuxostat in these studies were not systematic, because allopurinol was not dose-titrated above 300 mg/d in the comparison studies, whereas febuxostat was employed at doses between 40 and 240 mg/d (5,34,35). A consistent finding has been that febuxostat at 80 mg/d and above is more effective than allopurinol 300 mg/d in achieving a serum urate level lower than 6 mg/dL in gout patients [35]. However, early gout flare rates (under conditions where colchicine prophylaxis was stopped prematurely) were higher in patients treated with more than 80 mg/d of febuxostat (in association with more profound lowering of serum urate level) [5]. At 1 year, gout flare rates decline over time comparable to patients treated with allopurinol 300 mg/d and febuxostat 80 or 120 mg/d, and tophus size becomes reduced by 50% to 80% after 1 year in these treatment groups [5]. Greater tophus and gout flare reduction was associated with greater serum urate level lowering in these treatment groups. In an open-label extension study in which patients could be switched to febuxostat to achieve a serum urate level lower than 6 mg/dL, about 50% of febuxostat-treated patients with tophi demonstrated elimination of tophi by 2 years. Analysis of detailed comparisons of effects on quality of life in such studies would be of great interest.

In a recent, large, phase 3 trial, doses of 40 and 80 mg/d of febuxostat were compared with 300 mg/d of allopurinol, with inclusion of subjects with moderate renal insufficiency (CrCl, 30–59) treated with allopurinol, 200 mg/d [35]. In this study, serum urate-lowering effects were similar for 40 mg/d of allopurinol and febuxostat. However, 80 mg/d of febuxostat was significantly better than 40 mg/d of febuxostat and allopurinol in the attainment of a serum urate level

lower than 6 mg/dL, with this result including the subset of patients with CKD [35].

Febuxostat is a selective xanthine oxidase inhibitor that, unlike allopurinol, is neither reincorporated into purine nucleosides nor interferes with pyrimidine metabolism. This distinction is noteworthy. For example, allopurinol nephrotoxicity in rats is mediated by effects on pyrimidine metabolism [36]. Potentially, other allopurinol adverse events could be mediated by nonselective effects on purine and pyrimidine metabolism. In addition, febuxostat is primarily metabolized by oxidation and glucuronidation in the liver, in contrast to the primary renal elimination of oxypurinol, the principal active allopurinol metabolite. These theoretic advantages of febuxostat relative to allopurinol are particularly pertinent to CKD. However, careful study and analysis is needed to define best clinical practice for choosing between upward dose titration of allopurinol compared with other options, such as substitution of febuxostat (or uricase therapy) [2•,3,8,27••,33••].

We must define how to time these choices and choose upper limits of daily allopurinol dose in patients (with and without CKD) who fail to meet an appropriate serum urate-lowering benchmark on current standard doses of allopurinol. In doing so, we must stay mindful that the objectives of serum urate-lowering therapy are not simply the reduction of serum urate. They also involve ultimate successful, safe, and cost-effective dissolution of tophi, elimination of acute and chronic gouty synovitis and associated pain and connective tissue degradation, and the patient-centered goals of reduction in functional, occupational, and social disability [2•].

Conclusions

Current evidence for best practice allopurinol use in CKD is to slowly but steadily increase the dose of allopurinol to achieve a serum urate target level of less than 6 mg/dL in patients who have demonstrated tolerance of allopurinol in the first few months of therapy, and to monitor judiciously for allopurinol tolerance and toxicity during and after dose titration. Currently, maximum tolerable doses of allopurinol are not established relative to differing degrees of renal impairment. Risk factors for AHS include CKD, concomitant thiazide diuretic use, presence of HLAB-58 (and in particular, the HLA-5801 allele in subjects of Han Chinese ancestry), and recent onset of allopurinol use. There is no evidence that restricting daily maintenance allopurinol doses to levels previously advocated by Hande et al. [10] eliminates AHS risk. The ability to switch patients with CKD and persistent hyperuricemia failing \leq 300 mg/d of allopurinol to new, advanced, urate-lowering therapeutics is a major medical advance. Cost effectiveness, safety, quality of life, and other outcome measures of such strategies, relative to continuing allopurinol dose titration upwards, require further study. Given that we do not adequately

understand the long-term safety of allopurinol at doses more than 300 mg/d in patients with CKD, individualization of the urate-lowering strategy is advised for patients with the combination of gout and moderate to severe CKD (CrCl < 60), with cautious monitoring for allopurinol safety.

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No further conflict of interest relevant to this article was reported.

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