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Pharmacologic Treatment of Gout Now and in the Future

Amy Carr, PharmD

Often nicknamed the "disease of kings," acute gout attacks are far from regal.[1] Gout remains the most common inflammatory arthritis with 3.9% of adults in the United States self-reporting gout.[2] The rise in the prevalence of gout over the past several decades has been attributed to dietary trends, increased prevalence of comorbidities, and increased use of diuretics for the management of cardiovascular diseases.[3] Although several effective approaches to gout and hyperuricemia are widely available, current treatment approaches are not always implemented optimally and many patients are not adherent to prescribed therapy.[4]

In addition to the direct consequences of gout such as pain and decreased quality of life, there is emerging evidence that hyperuricemia may be an independent risk factor for cardiovascular and renal disease. It has been hypothesized that allopurinol may have a cardioprotective effect in addition to the benefits conferred by reducing serum uric acid (sUA). In studies, allopurinol has been shown to reduce blood pressure[5] and observational studies have suggested an association between allopurinol use and reduced risk of MI.[6] Among patients with gout and heart failure, allopurinol has been associated with reduced heart failure readmissions or death and reduced all-cause mortality.[7] Whether these possible benefits are related to allopurinol use, specifically, or more generally to urate-lowering therapy is not known. Nevertheless, findings such as these have propelled development of novel drugs for gout, especially agents which will be effective and safe in the management of patients with comorbid conditions and particularly resistant gout.[8]

Treatment Strategies

The American College of Rheumatology (ACR) published their first recommendations for the treatment of gout in 2012.[9] The publication has two parts: part 1 covers nonpharmacologic and pharmacologic therapies for hyperuricemia,[9] while part 2 addresses therapy and anti-inflammatory prophylaxis of acute gouty arthritis.[3] This review focuses on the former – that is, management of hyperuricemia and prevention of gout.

Nonpharmacologic Approaches

All patients with gout should receive education regarding lifestyle modifications including weight loss, exercise, and smoking cessation to improve management of comorbidities such as coronary artery disease, obesity, metabolic syndrome, diabetes mellitus, hyperlipidemia, and hypertension.[9] Lifestyle modifications, such as limiting intake of purine-rich foods, may reduce sUA levels by 10-18%. Purine-rich foods include seafood, alcohol, and high fructose soft drinks.[10]

Chronic Gout Management

Pharmacologic therapy to lower sUA concentration should be started in the following patients: (1) patients with gout and tophus on clinical exam or imaging, (2) ≥2 acute gout attacks per year, (3) stage 2 or worse CKD, or (4) past urolithiasis. Initiation of urate-lowering therapy should always be accompanied by prophylactic anti-inflammatory therapy. First-line anti-inflammatory prophylaxis is oral low-dose colchicine or a low-dose NSAID. Low-dose NSAID therapy may be combined with a proton-pump inhibitor for prevention of peptic ulcer disease in appropriate patients. Second-line therapy in patients inadequately treated by colchicine or NSAIDs is low-dose systemic corticosteroids such as prednisone or prednisolone. Appropriate dosing for anti-inflammatory prophylaxis is summarized in **Table 1**. Anti-inflammatory prophylaxis should continue until the target sUA concentration is achieved and there is no clinical evidence of gout activity. Prophylactic therapy should be continued for ≥6 months, 3 months after achieving target sUA concentrations without tophi present, or 6 months after achieving target sUA concentrations in the presence of 1 or more tophi. Counseling patients that this strategy reduces, but does not eliminate attacks is highly important as patient frustration with acute gout attacks during initiation of urate-lowering therapy may contribute to nonadherence.[3]

First-line urate-lowering therapy is a xanthine oxidase inhibitor with the goal to achieve target sUA concentrations and improve signs and symptoms. Xanthine oxidase inhibitors work to decrease uric acid production by inhibiting the conversion of hypoxanthine to xanthine and xanthine to uric acid.[10] Two xanthine oxidase inhibitors, allopurinol and febuxostat, are marketed in the U.S. and, when dosed adequately, these agents likely have similar efficacy. Febuxostat and allopurinol may be substituted for each other in cases of drug intolerance, adverse events, or failure of initial therapy. A summary of dosing for xanthine oxidase inhibitors can be found in **Table 1**.

The starting dose of allopurinol should be ≤100 mg per day. For patients with stage 4 or worse CKD, 50 mg is a reasonable

Table 1 | Dosing of Current Drug Therapy.[3,9,10,23-25]

Anti-inflammatory Attack Prophylaxis	
First Line:	
Colchicine	0.5-0.6 mg daily or twice daily
NSAIDs	
Naproxen	250 mg twice daily
Second Line:	
Prednisone	≤10 mg daily
Prednisolone	≤10 mg daily
Chronic Gout Treatment	
First Line:	
Xanthine Oxidase Inhibitors	
Allopurinol	*Initial*: ≤100 mg daily *Maximum*: 800 mg daily in divided doses
Febuxostat	*Initial*: 40 mg daily *Maximum*: 80 mg daily per FDA; 120 mg daily per ACR
Second Line:	
Uricosuric Agents	
Probenecid	*Initial*: 250 mg twice daily for 1 week, then 500 mg twice daily *Maximum*: 2,000 mg daily
Third Line:	
Pegloticase	8 mg IV every 2 weeks for ≥6 months

ACR = American College of Rheumatology; **IV** = intravenous.

starting dose. Initiating allopurinol at a low dose may reduce occurrence of early gout flares as often seen with the initiation of urate-lowering therapy. Although data are limited, starting with a low dose of allopurinol may also reduce the risk of hypersensitivity reactions and allopurinol hypersensitivity syndrome (AHS). While the incidence of AHS is only 1 in 1,000 in the U.S., the consequences of AHS can be grave. AHS may cause Stevens-Johnson syndrome, toxic epidermal necrolysis, eosinophilia, vasculitis, rash, and major end-organ damage.[9] Unfortunately, 83% of patients initiated on allopurinol, especially those without renal impairment, do not have their sUA concentration measured or their dose titrated in the first 6 months.[4] In the U.S., the vast majority of patients are titrated only to ≤300 mg daily, possibly because of concerns over a higher risk of AHS in patients with CKD using higher doses of allopurinol. However, existing data do not support this concern and studies have shown that only 35-40% of patients reach target sUA concentrations of <6.0 mg/dL with conventional allopurinol dosing of up to 300 mg daily.[11] Allopurinol is largely well-tolerated and should be titrated up as needed to achieve target sUA concentrations, even in those with CKD.[10] The FDA-approved maximum dose of allopurinol is 800 mg daily, but even titrating up to 600 mg daily may achieve target uric acid concentrations in up to three-quarters of patients.

Febuxostat was developed initially as an alternative to allopurinol for patients who were unable to tolerate allopurinol or unable to achieve adequate doses due to renal impairment.[11] Advantages to febuxostat over allopurinol have been suggested to include better efficacy in patients with mild to moderate renal impairment and fewer drug-drug interactions. However, it is worth noting that comparative trials between febuxostat and allopurinol have often used suboptimal fixed-dosing of allopurinol, thus limiting ability to truly compare these agents. Indeed, no published studies comparing the efficacy of febuxostat and allopurinol have used mean allopurinol doses >300 mg daily. Limitations to the use of febuxostat include high cost and elevated liver function tests.[10]

In a retrospective analysis of 226 women with gout, Chohan, et al., found that febuxostat 80 mg daily may be more efficacious than allopurinol at the commonly prescribed (and often suboptimal) doses of 100 to 300 mg daily. In this study, 85.1% of females taking febuxostat 80 mg daily achieved a sUA concentration of <6.0 mg/dL as compared to 45.9% of females taking allopurinol. This statistically significant difference between febuxostat and allopurinol provides further evidence that allopurinol at doses of <300 mg daily does not effectively achieve target sUA concentrations in the majority of patients.[12] Among patients with an inadequate response to allopurinol, defined as not achieving target sUA concentrations, Stamp, et al., found the two most common causes to be poor adherence and underdosing.[13]

In a retrospective study of records for 16,040 patients with commercial and Medicare Advantage health plans, Singh, et al., found that febuxostat was more effective than allopurinol at lowering sUA concentrations. Patients taking febuxostat achieved target sUA concentrations more frequently and more quickly than patients taking allopurinol. Of note, 97% of patients in this study were receiving ≤300 mg per day of allopurinol. The majority of patients on febuxostat were receiving 40 mg per day.[14] While this study provides valuable insight, it is difficult to draw major conclusions since the study was retrospective and many of the patients, especially those on allopurinol, may have been underdosed.

Becker, et al., conducted a multi-center, randomized control trial of 760 patients with sUA concentrations of 8.0 mg/dL or greater to compare the safety and efficacy of febuxostat and allopurinol. Following a two week washout period, patients were randomly assigned to receive febuxostat 80 mg daily, febuxostat 120 mg daily, or allopurinol 300 mg daily for one year. The primary endpoint was sUA concentration of <6.0 mg/dL in the final three monthly measurements. There was a statistically and clinically significant difference ($p<0.001$) between the patients taking febuxostat at either dose and the patients taking allopurinol. Of patients taking febuxostat, 53% of those at the 80 mg daily dose and 62% of those at the 120 mg daily dose achieved a sUA concentration of <6.0 mg/dL. Conversely, only 21% of patients receiving allopurinol achieved target urate concentrations. Naproxen or colchicine was provided as acute flare prophylaxis during the first eight weeks of therapy with either xanthine oxidase inhibitor. There was no clinically or statistically significant difference in the number of gout flares or the area and number of tophi experienced by patients taking febuxostat at either dose or allopurinol. With reference to safety, patients in all groups reported similar frequency and severity of adverse events. Abnormal liver-function tests were the most common reason for withdrawal from the study with a statistically higher number of patients in the febuxostat 120 mg daily group being affected than the allopurinol group.[15]

A review by Jennings, et al., of the first 400 patients enrolled in the Febuxostat versus Allopurinol Streamlined Trial (FAST) found that 144 patients (36%) had a sUA concentration above

target at screening. This study found that patients requiring up-titration were more likely to be male, have a higher BMI, have higher alcohol intake, be prescribed a diuretic, and have a lower daily dose of allopurinol. At the time of screening, only 2% of patients were prescribed a daily dose of allopurinol that was greater than 300 mg. In patients with a sUA concentration above 6.0 mg/dL, allopurinol was up-titrated by 100 mg daily every two weeks until the patient achieved the goal concentration. This process of up titrating the allopurinol dose did not result in any serious adverse events or lead to the discontinuation of allopurinol. Ninety-seven percent of these patients were able to achieve target sUA concentrations and the median dose required was 300 mg daily with a maximum required allopurinol dose of 700 mg daily. Less than 10% of patients required a dose greater than 400 mg daily to achieve target levels. Reported adverse effects included dry mouth and mildly elevated liver function tests – none of which required a dose change or drug discontinuation. All patients requiring up-titration of their allopurinol dose were offered prophylaxis for gout flares in the form of colchicine or an NSAID. Only three of the 144 patients (2%) experienced a gout flare during the up-titration period and all three patients were taking gout flare prophylaxis.[16]

After xanthine oxidase inhibitor initiation, sUA concentrations should be monitored every two to five weeks and urate-lowering therapy should be titrated until the target sUA level is achieved. Target sUA level for all patients should be at least <6 mg/dL with a target of <5 mg/dL, especially for patients who remain symptomatic with concentrations <6 mg/dL. The lower the sUA concentration, the less likely the uric acid is to crystalize and precipitate in the joints. Once target level is achieved, sUA concentrations may be checked every six months.[9]

In patients unable to tolerate upward titration or achieve target sUA concentrations even after appropriate dose titrations, switching from one xanthine oxidase inhibitor to another should be considered. A uricosuric agent should be added in patients who are still unable to achieve target sUA concentrations. Uricosuric agents increase the urinary excretion of uric acid and contraindications to these agents include history of urolithiasis and elevated urine uric acid concentrations.[10] The uricosuric agent of choice in the U.S. is probenecid. For patients with contraindications or intolerance of xanthine oxidase inhibitors and a creatinine clearance >50 mL/min, probenecid is an alternative first-line agent.[9] **Table 1** provides dosing recommendations for probenecid. Theoretically, the effectiveness of probenecid may decrease with declining renal function but data addressing this issue are limited and suggest there may be no loss of effectiveness.[8] Because patients with gout often have chronic comorbidities, consideration may be given to agents with uricosuric properties in the treatment of these other diseases. For example, for patients with an indication for angiotensin receptor blocker therapy, losartan may be preferred because of its uricosuric properties. Previous studies have shown significant reductions in sUA with this agent, but not irbesartan or candesartan.[17] Furthermore, when combined with hydrochlorothiazide, losartan appears to overcome the thiazide-induced elevation in uric acid. Likewise, if a fibrate is indicated for patients, fenofibrate may be preferred given that a previous study highlighted an increased excretion of uric acid in the urine of patients with hyperuricemia and dyslipidemia taking fenofibrate monotherapy as well as fenofibrate and losartan combination therapy.[18] A similar meta-analysis reviewed patients with normal baseline sUA levels revealed that fenofibrate significantly reduced sUA concentrations.[19]

In patients with severe, refractory gout despite an appropriately-dosed xanthine oxidase inhibitor and a uricosuric agent, a synthetic uricase may be appropriate to facilitate conversion of uric acid to allantoin to facilitate urinary excretion.[10] The addition of a synthetic uricase can lead to dramatic reductions in sUA as well as decrease the number and size of tophi.[8] Pegloticase is the only FDA-approved synthetic uricase for the treatment of gout. Pegloticase is administered intravenously every two weeks and is prone to infusion reactions in 20% to 40% of treated patients.[8,9] Additional concerns related to treatment with pegloticase include a possible increased risk of cardiovascular events, but this finding needs to be investigated further.[8] Dosing recommendations for pegloticase in the treatment of gout are summarized in **Table 1**. Rasburicase, another synthetic uricase, is only indicated for hyperuricemia associated with chemotherapy.[10,20] Largely because of the intravenous administration and higher cost, the use of synthetic uricases has been limited to the most serious and difficult cases of gout in which patients are unable to achieve target levels and symptomatic relief with oral therapy.

Newer Agents

Despite the lengthy history of gout, treatment options are relatively limited. Many of the currently available agents are prone to drug-drug interactions and unfavorable side effects. In addition, the use of many of the current agents is limited in patients with poor renal function as is common in patients with gout. Consequently, many patients with gout remain inadequately treated and might benefit from the discovery and development of novel agents.

In addition to the recently approved agent, lesinurad (Zurampic®), there are several new agents with novel mechanisms of action currently in Phase II and Phase III trials (**Table 2**). The majority of the new agents in development are focused on preventing urate reabsorption in the proximal tubule through inhibition of URAT1, Organic Anion Transporter 4 (OAT4), and glucose transport 9 (GLUT9) in the kidneys.[10]

Lesinurad

Lesinurad (Zurampic®) is a recently approved selective uric acid reabsorption inhibitor (SURI). By inhibiting URAT1, lesinurad prevents the reabsorption of urate in the proximal renal tubule. Lesinurad also inhibits OAT4 in the renal tubule and leads to reduced uric acid levels, even in patients on diuretic therapy. This mechanism is especially important for hypertensive patients on thiazide diuretic therapy, which typically exacerbates hyperuricemia. In Phase II studies, lesinurad has been studied in combination with allopurinol as well as in combination with febuxostat. As discussed below, adding lesinurad to a xanthine oxidase inhibitor lead to significant reductions in sUA with limited adverse events. Similar to other urate-lowering therapies, lesinurad has been associated with gout flares during early treatment initiation.[10]

In a published Phase II study of patients with an inadequate response to allopurinol, patients were randomly assigned to receive four weeks of treatment with (1) lesinurad 200 mg daily + allopurinol, (2) lesinurad 400 mg daily + allopurinol, (3) lesinurad 600 mg daily + allopurinol, or (4) placebo + allopurinol. An inadequate response to allopurinol was defined as a sUA concentration ≥6 mg/dL on ≥2 occasions that were ≥2 weeks apart. All patients were maintained on their baseline dose of allopurinol, which ranged from 200-600 mg and was ≥300 mg for the majority of patients. For the lesinurad 200 mg daily (the dose that was ulti-

Table 2 | Recently Approved and Investigational Agents.[11,21,26]

Drug	Mechanism of Action	Estimated Urate-Lowering Ability (%)	Status
Lesinurad (Zurampic®)	Increases uric acid excretion • URAT1 and OAT4 inhibitor	15-30%	FDA-approved (December 2015) in combination with allopurinol
Arhalofenate	Increases uric acid excretion • URAT1 and OAT4 inhibitor • Peroxisome proliferator-activated receptor-ligand (PPAR)-c modulator	20-40%	Phase III Trials
Ulodesine	Reduces uric acid production • Purine nucleoside phosphorylase (PNP) inhibitor	unknown	Phase II Trials

mately approved by FDA) + allopurinol treatment group, the mean baseline sUA concentration was 6.37 prior to starting lesinurad. This group saw a mean reduction is sUA of 16.1% as compared to a mean increase of 2.6% for the placebo group. Despite all patients being required to take colchicine for flare prophylaxis, 21.7% of patients on lesinurad 200 mg daily reported a gout flare as compared to 20.8% of patients taking placebo. Similarly, headache, arthralgias, and nasopharyngitis, were reported at rates similar to placebo. There were no serious adverse events or deaths and the only three patients who discontinued therapy because of treatment-related adverse events were taking lesinurad doses greater than 200 mg. This study included patients with stage 2 chronic kidney disease and concluded that lesinurad can be used safely and effectively in this patient population. Although lesinurad is hepatically metabolized and renal dysfunction has not been shown to increase plasma concentrations of lesinurad, further research needs to be conducted into the safety and efficacy of this agent in patients with more severe renal dysfunction.[21]

Lesinurad has also been studied in combination with febuxostat. In an open-label study of 21 patients who received febuxostat 40 mg daily or 80 mg daily for seven days followed by febuxostat with lesinurad 400 mg daily for seven days, and then febuxostat in combination with lesinurad 600 mg daily for seven days. Patients in group 1 (febuxostat 40 mg daily) had a mean baseline sUA concentration of 9.2 mg/dL and patients in group 2 (febuxostat 80 mg daily) had a mean baseline sUA concentration of 10.4 mg/dL. For the initial part of the study with febuxostat monotherapy, 67% percent of group 1 patients and 56% of group 2 patients achieved sUA concentrations <6.0 mg/dL. The addition of lesinurad at either dose to patients on either febuxostat dose (i.e., either group) lead to 100% of patients achieving sUA concentration of <5.0 mg/dL.[11,22]

Lesinurad has been approved by the FDA at a dose of 200 mg daily in combination with a xanthine oxidase inhibitor (allopurinol or febuxostat). With the novel mechanism of this agent and its recent approval, the place in therapy for lesinurad is yet to be determined. With the majority of cases being caused by underexcretion of uric acid, many believe combination therapies are the future since they work to prevent uric acid synthesis as well as increase urinary excretion.[11]

Arhalofenate

Arhalofenate, another agent in clinical trials, also inhibits URAT1 and OAT4 in the renal tubule, but additionally is a peroxisome proliferator-activated receptor-ligand (PPAR)-c modulator. Arhalofenate was originally developed and investigated for treatment of hyperglycemia. The early data from Phase II trials of arhalofenate suggest a dose-dependent reduction in sUA concentrations, even in patients taking diuretics. Phase II trials of arhalofenate in both diabetic and healthy patients have shown decreases in sUA levels by 20-40% despite the majority of patients having normal uric acid concentrations at baseline. Excitingly, it does not appear that the uricosuric effect of arhalofenate decreases as renal function declines. This could provide an alternative option to the currently marketed uricosuric agent, probenecid.[11] Additional Phase II and Phase III studies of arhalofenate monotherapy as well as in combination with a xanthine oxidase inhibitor are the next steps for this potential new drug.[8]

Urate Synthesis Inhibitors

Ulodesine is a purine nucleoside phosphorylase (PNP) inhibitor in Phase II trials. Inhibition of PNP prevents the conversion of purines to hypoxanthine which ultimately decreases the synthesis of uric acid. Thus far, ulodesine has been studied and shown efficacy as both monotherapy and in combination with allopurinol, although these phase II trials have not been published at the time of this writing. In a study of ulodesine monotherapy in patients with baseline sUA concentrations >8.0 mg/dL, 30% of patients receiving 80 mg daily and 77% of patients receiving 240 mg daily achieved sUA concentrations <6.0 mg/dL. Despite higher doses of ulodesine causing more diarrhea (20%) and rash (13%), adverse events did not occur significantly more than placebo.[11] In a Phase II trial of patients taking ulodesine 40 mg daily in combination with allopurinol 300 mg daily, 100% of patients were able to achieve sUA concentrations of <6.0 mg/dL. As a PNP inhibitor, there is concern that this agent would negatively impact the immune system as the absence of PNP is associated with immunodeficiency and autoimmune disorders. To date, this agent has not been found to cause more infections or lead to a greater reduction in lymphocyte count than placebo. Ulodesine would represent an entirely new class of drugs and a novel approach to the treatment of hyperuricemia.[8,11]

Summary

Despite an extensive history, current treatments for gout are imperfect and their implementation into practice is often suboptimal.[4] However, there has been a recent rise in focus on appropriate urate-lowering therapy as evidence emerges that hyperuricemia may increase a patient's risk of cardiovascular disease and renal dysfunction. With data demonstrating that currently available agents, especially allopurinol, are efficacious and safe when optimally dosed, there should be a drive to improve guideline adher-

ence in order to improve patient outcomes. The recent approval of lesinurad along with the promising Phase II and Phase III studies of investigational agents, such as arhalofenate and ulodesine, provide reason to be optimistic about the future of chronic gout therapy.

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