

Long-term Treatment of Gout: New Opportunities for Improved Outcomes

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CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

- Make a presumptive diagnosis of gout based on history and physical examination
- Individualize and modify urate-lowering therapy based on best evidence to achieve treatment goals

TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding primary care management of the long-term treatment of gout.

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Release Date: 1 August 2018
Expiration Date: 31 July 2019

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This article is supported by an educational grant from Ironwood Pharmaceuticals, Inc.

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DISCLOSURES

Dr. Doghramji discloses that he is on the advisory board for Ironwood Pharmaceuticals, Inc.; and owns stock in Pfizer Inc.

ACKNOWLEDGEMENT

Editorial support was provided by Gregory Scott, PharmD, RPh, and Angela Cimmino, PharmD. The author was responsible for all content and editorial decisions.

SUPPORT

This article is sponsored by Primary Care Education Consortium and supported by funding from Ironwood Pharmaceuticals, Inc.

WHAT DO THE 3 FOLLOWING REAL-LIFE CASES HAVE IN COMMON?

1. An adult male presenting with pain in the foot and instep
2. A postmenopausal female presenting with wrist pain and stiffness
3. A young, thin male presenting with severe pain in the mid-foot, similar to what his father and brother experience.

The underlying cause of pain in all 3 of these patients is undiagnosed gout, demonstrating different presentations of gout.

This article will discuss some of the key questions and clinical challenges encountered in the long-term primary care management of patients with gout.

ARE THERE CONSEQUENCES OF GOUT BEYOND IMPAIRED FUNCTIONING AND QUALITY OF LIFE?

Gout is an independent predictor of premature death and is associated with a high frequency of comorbidities, many with a prevalence 2 to 3 times higher than among people without gout: hypertension, chronic kidney disease (CKD), obesity, type 2 diabetes, nephrolithiasis, cardiac disease (including coronary artery disease, heart failure, and atrial fibrillation), dyslipidemia, stroke, peripheral arterial disease, and sleep apnea.¹⁻³

DO ALL PATIENTS WITH HYPERURICEMIA DEVELOP GOUT?

Based on an estimated prevalence of gout of 3.9% (8.3 million) and hyperuricemia (ie, serum uric acid [sUA] level >7.0 mg/dL in men and >5.7 mg/dL in women) of 21.4% (43.3 million) among US adults, approximately 1 in 5 people with hyperuricemia develop symptoms of gout.⁴ Although the prevalence of hyperuricemia is similar among men (21.2%) and women (21.6%), the prevalence of gout is approximately 3 times higher in men than in women (5.9% and 2% of adults in the United States, respectively); the disparity between sexes lessens after menopause.⁵ The overall prevalence of gout increases with age, from 3.3% in adults over the age of 40 years to 9.3% in adults over the age of 70 years.⁴ Family history may also play a small role.

CASE STUDY, STEVE:

A 37-year-old male with obesity (body mass index, 33 kg/m²) presents with a painful, swollen big toe. He has a family history of gout (father, brother). sUA is 7.3 mg/dL.

WHAT ARE THE COMMON FINDINGS ON HISTORY AND PHYSICAL EXAMINATION THAT SUGGEST GOUT?

An acute gout attack (flare) is typically monoarthritic early in the disease and peaks within hours, manifesting as a severely inflamed joint that is red, hot, swollen, and tender to the touch or movement.⁶ The attack is self-limiting, with symptoms resolving within about 2 weeks, although ongoing joint damage during intercritical asymptomatic periods usually occurs due to continuing monosodium urate (MSU) crystal deposition and inflammation.⁷ An acute attack most commonly manifests in the lower extremities, particularly the first metatarsophalangeal joint (podagra) in men, whereas the elbow, wrist, and hands are more likely to be affected in women.^{6,8} The reduced solubility of urate at lower temperatures may account for the occurrence of gout at peripheral joints, which are cooler than central-axis

joints.⁹ Involvement of more than 1 joint is more common as disease progresses.⁶

WHAT, IF ANY, FURTHER ASSESSMENT IS NEEDED BEYOND THE HISTORY AND PHYSICAL EXAMINATION TO CONFIRM THE DIAGNOSIS OF GOUT?

The most important component of the differential diagnosis of acute gout is septic arthritis, although the incidence of septic arthritis is much lower. In addition, the onset of septic arthritis is more insidious, and patients with septic arthritis tend to be quite sick with fever, rash, or other signs of systemic illness, and typically require hospitalization.^{8,10}

Synovial fluid aspiration and identification of MSU crystals by polarized light microscopy is the gold standard of gout diagnosis.⁶ However, an adequate clinical analysis is sufficient for diagnosis in most cases, so this test is often not required.¹¹ Combined with intra-articular corticosteroid injection, joint aspiration provides immediate and lasting pain relief for many patients.^{6,8} Radiography is not useful in early gout because small erosions and tophi are difficult to detect, but such lesions are detectable in chronic gout.⁶ Although not commonly done, ultrasonography is useful in early gout to distinguish between active and inactive tophi.⁶

The absence of hyperuricemia is inadequate alone to rule out a gout diagnosis because the sUA level may drop to normal during a gout attack. Therefore, even though it is reasonable to measure sUA during an attack, the sUA level should be measured again several weeks after the flare has resolved.¹⁰ It should be kept in mind that each laboratory calculates its own sUA threshold for hyperuricemia, so a "normal" sUA level may, nevertheless, reflect levels in joint tissues that are above ~6.8 mg/dL necessary for MSU crystal deposition.⁷ Most labs these days will also list, "sUA desirable level for gout treatment: <6.0 mg/dL."

Hyperuricemia and gout should be considered red flags for metabolic syndrome and cardiovascular disease. Therefore, additional evaluation includes a comprehensive metabolic panel (eg, blood glucose and hemoglobin A1c levels and kidney and liver function) and a lipid panel, as well as clinical screening for associated comorbidities and cardiovascular risk factors (eg, obesity, hypertension, smoking).^{12,13}

CASE STUDY, STEVE (CONTINUED)

A diagnosis of gout is confirmed. A plan is developed to begin a nonsteroidal anti-inflammatory drug for acute treatment for the flare. Once the flare has resolved, urate-lowering therapy will be initiated.

WHAT ARE THE OBJECTIVES OF LONG-TERM GOUT MANAGEMENT?

Monosodium urate crystal formation is reversible, and crystals will dissolve when the sUA level drops below the limit of solubility (~6.8 mg/dL). This will result in the disappearance of gout flares and a reduction in the size and number of tophi.^{12,14} The lower the sUA level, the faster the crystal deposits (and tophi) resolve. Therefore, the goal of long-term gout management is to lower the sUA level below the limit of solubility.¹⁴ In addition, the management of patients with gout should include prevention and treatment of associated cardiovascular and other diseases.³

WHAT IS THE TARGET SUA GOAL?

According to both the American College of Rheumatology (ACR) guidelines and the European League Against Rheumatism (EULAR) recommendations, the target sUA goal for urate-lowering therapy (ULT) is <6 mg/dL for all gout patients. A lower sUA target (<5 mg/dL) to facilitate faster dissolution of crystals is recommended for patients with severe gout (tophi, chronic arthropathy, frequent attacks) until total crystal dissolution and resolution of gout are achieved.^{12,15}

Appropriately treated gout, with maintenance of sUA below target levels, markedly reduces the frequency of gout flares and the size and number of tophi and improves quality of life (QoL).¹² Inadequate treatment that fails to maintain sUA below target levels is associated with recurrent flares, further joint damage, and subsequent loss of mobility, functional impairment, and decreased QoL.¹¹

HOW OFTEN SHOULD SUA BE MONITORED?

The American College of Radiology guidelines recommend monitoring sUA every 2 to 5 weeks during ULT titration (see “How is each of the approved ULTs initiated and titrated?” on page S23), then every 6 months once the sUA target level is achieved.¹⁵

DOES LIFESTYLE MANAGEMENT HAVE A ROLE?

Evidence from randomized, blinded studies is lacking regarding alteration of lifestyle factors translating into improved outcomes in patients with gout. However, diet, exercise, and weight loss have been associated with a modest reduction in the sUA level in some clinical trials; therefore, every patient should be encouraged to make such changes as best as possible.^{12,15} Lifestyle management (eg, reducing excess body weight, regular exercise, smoking cessation, and avoiding excessive alcohol and sugar-sweetened drinks) has a greater role in reducing the risk and optimizing management of life-threatening comorbidities in patients with gout.^{12,13,15}

WHAT MEDICATIONS ARE APPROVED IN THE UNITED STATES AS ULT? WHAT IS THE MECHANISM OF ACTION OF EACH MEDICATION?

Available US Food and Drug Administration (FDA)-approved options for lowering sUA include xanthine oxidase inhibitors (allopurinol and febuxostat) that prevent production of uric acid; a uricosuric agent (probenecid) that increases uric acid output in urine; and a uric acid-specific enzyme (pegloticase) that converts uric acid to allantoin. Another recently approved uricosuric agent, lesinurad, inhibits the function of transporter proteins (urate transporter 1 and organic anion transporter 4) involved in uric acid reabsorption in the kidney.^{6,16}

Fenofibrate, losartan, and atorvastatin are not FDA-approved for gout but act as uricosurics and can therefore be used to treat gout comorbidities or in association with xanthine oxidase inhibitors.⁶ There has been limited study of rasburicase, an injectable approved for tumor lysis, in the treatment of tophaceous gout.¹⁶

CASE STUDY, HARRIET:

In a patient diagnosed with gout (and who has normal renal function), allopurinol, 300 mg daily, is initiated after resolution of an acute flare. sUA is reduced from 8.6 mg/dL to 7.2 mg/dL after 9 months of treatment. Clinical decision points:

- Should the dosage of allopurinol be increased or should a non-xanthine oxidase inhibitor be initiated?
- If the patient's estimated glomerular filtration rate is 35 mL/min/1.73 kg/m², would this impact the decision between uptitrating and adding a second agent?

WHAT ARE THE RECOMMENDATIONS AND EVIDENCE FOR EACH ULT?

Guidelines recommend a xanthine oxidase inhibitor as first-line therapy.¹⁵ Allopurinol is most commonly used due to its low cost, extensive clinical experience, and relatively good safety and efficacy profile.^{8,13}

For patients who do not achieve the target sUA level with optimized allopurinol therapy, the next-step choice is primarily a consideration of patient-specific factors, physician and patient choice, and cost. In the author's experience, a good option is using medications with different mechanisms of action because this provides further lowering of sUA while enabling the use of lower dosages of individual medications, thereby reducing the incidence and severity of dosage-related adverse events.

The xanthine oxidase inhibitor febuxostat, 80 mg/d or 120 mg/d (the latter an investigational dose but recommended by ACR and EULAR when needed) has demonstrated superior urate-lowering efficacy compared with allo-

TABLE Key studies of urate-lowering therapy^{18,19,22-25}

• Study/author • Baseline sUA level • Prior treatment	Treatment	Primary efficacy result
<ul style="list-style-type: none"> FACT/Becker¹⁸ Mean sUA, 9.8-9.9 mg/dL ALP (44% of subjects) 	52 weeks ALP 300 mg/d (n=253) FBX 80 mg/d (n=256) FBX 120 mg/d (n=251)	<i>Percentage of patients with sUA <6 mg/dL at last 3 monthly measurements</i> ALP 300 mg/d: 21% FBX 80 mg/d: 53% ($P<.001$) ^a FBX 120 mg/d: 62% ($P<.001$) ^a
<ul style="list-style-type: none"> APEX/Schumacher¹⁹ Mean sUA, 9.85 mg/dL ALP (~1/3 of subjects) 	28 weeks ALP 300 mg/d (n=268) ^b FBX 80 mg/d (n=267) FBX 120 mg/d (n=269) FBX 240 mg/d (n=134) PBO (n=134)	<i>Percentage of patients with sUA <6 mg/dL at last 3 monthly measurements</i> ALP 300 mg/d: 22% FBX 80 mg/d: 48% ($P<.05$) ^a FBX 120 mg/d: 65% ($P<.05$) ^a FBX 240 mg/d: 69% ($P<.05$) ^a PBO: 0%
<ul style="list-style-type: none"> CLEAR 1/Saag²³ sUA, ≥ 6.5 mg/dL ALP ≥ 300 mg/d (≥ 200 mg/d in patients with moderate renal impairment) and ≥ 2 gout flares during the previous year 	12 months PBO/ALP (n=201) LSN 200 mg/d + ALP (n=201) LSN 400 mg/d + ALP (n=201)	<i>Percentage of patients with sUA <6 mg/dL at 6 months</i> PBO/ALP: 27.9% LSN 200 mg/d + ALP: 54.2% ($P<.0001$) ^a LSN 400 mg/d + ALP: 59.2% ($P<.0001$) ^a
<ul style="list-style-type: none"> CRYSTAL/Dalbeth²² ULT-naïve: sUA, ≥ 8 mg/dL; ULT treated: sUA, ≥ 6 mg/dL 	12 months PBO/FBX 80 mg/d (n=109) LSN 200 mg/d + FBX 80 mg/d (n=106) LSN 400 mg/d + FBX 80 mg/d (n=109)	<i>Percentage of patients with sUA <5 mg/dL by month 6</i> PBO/FBX 80 mg/d: 46.8% LSN 200 mg/d + FBX 80 mg/d: 56.6% ($P=.13$) ^a LSN 400 mg/d + FBX 80 mg/d: 76.1% ($P<.0001$) ^a
<ul style="list-style-type: none"> Open label study/Reinders²⁴ N/A Benzbromarone 	Stage 1: 2 months ALP 200-300 mg/d (based on renal function) (n=32) Stage 2: >2 months Probenecid 1000 mg/d, added to ALP in patients failing to attain sUA <0.3 mmol/L ^c (n=14)	<i>Percentage of patients attaining sUA <0.3 mmol/L^c</i> Stage 1 ALP monotherapy: 25% Stage 2 ALP plus probenecid: 86%
<ul style="list-style-type: none"> CO405/Sundy²⁵ sUA, 9.4-10.4 mg/dL Intolerant or refractory to ALP 	6 months Group 1: Pegloticase 8 mg biweekly (n=43) Group 2: Pegloticase 8 mg monthly (n=41) Group 3: PBO (n=20)	<i>Percentage of patients with sUA <6 mg/dL $\geq 80\%$ of the time at Month 3 and Month 6</i> Group 1: 47% (95% CI, 31%-62%) Group 2: 20% (95% CI, 9%-35%) Group 3: 0
<ul style="list-style-type: none"> CO406/Sundy²⁵ sUA, 9.5-9.8 mg/dL Intolerant or refractory to ALP 	6 months Group 1: Pegloticase 8 mg biweekly (n=42) Group 2: Pegloticase 8 mg monthly (n=43) Group 3: PBO (n=23)	<i>Percentage of patients achieving sUA <6 mg/dL $\geq 80\%$ of the time at Month 3 and Month 6</i> Group 1: 38% (95% CI, 24%-54%) Group 2: 49% (95% CI, 33%-65%) Group 3: 0

^aCompared with allopurinol-based arm.^b10 subjects received 100 mg/d and 258 subjects received 300 mg/d, based on renal function.^csUA, 0.3 mmol/L = ~5.0 mg/dL.**Abbreviations:** ALP, allopurinol; CI, confidence interval; FBX, febuxostat; LSN, lesinurad; PBO, placebo; sUA, serum uric acid.

purinol at a fixed dosage of 300 mg/d (**TABLE**).^{12,17-19} Although ACR guidelines do not give preference to allopurinol or febuxostat, EULAR and other international guidelines recommend that febuxostat be used in patients who are intolerant of, or do not respond to, an adequate dosage of allopurinol.^{12,13,15} Febuxostat has been associated with cutaneous reactions, but data do not support any cross-reactivity with allopurinol.¹² Liver function abnormalities and a slightly higher incidence of cardiovascular thromboembolic events may occur.²⁰

Guidelines also recommend adding a uricosuric agent (lesinurad or probenecid) or switching to a uricosuric agent (probenecid) if the sUA target level cannot be reached by an appropriate dosage of a xanthine oxidase inhibitor or when a xanthine oxidase inhibitor is not tolerated.^{12,13,15} The efficacy of probenecid in combination with allopurinol in such patients has been demonstrated in a few small trials.²¹ However, probenecid is not recommended in patients with a creatinine clearance <50 mL/minute or uric acid urolithiasis.¹⁵

Lesinurad is approved only as add-on therapy to a xanthine oxidase inhibitor.¹⁶ In large, randomized clinical trials, lesinurad in combination with either allopurinol or febuxostat has demonstrated greater efficacy than either of the xanthine oxidase inhibitors as monotherapy (**TABLE**).^{18,19,22-25} Lesinurad has been associated with a transient elevation of serum creatinine and kidney stones, the incidence of which is higher if taken without a xanthine oxidase inhibitor.

Pegloticase can be considered in patients with crystal-proven severe, debilitating chronic tophaceous gout and poor QoL, in whom the sUA target level cannot be reached with any other available drug at the maximal dosage (including combination therapy).¹² Pegloticase is an IV medication that must be given at an appropriately trained infusion center because there is a risk of anaphylaxis.

The **TABLE** summarizes results of key clinical trials for ULT agents approved in the United States.^{18,19,22-25}

HOW IS EACH OF THE APPROVED URATE-LOWERING MEDICATIONS INITIATED AND TITRATED?

A treat-to-target approach should be utilized, whereby ULT is initiated and intensified as needed to achieve and maintain the target sUA level <6 mg/dL, or ≤5 mg/dL in certain patients (eg, those with tophi), as discussed.^{12,15} Because initiation of ULT is associated with gout flares for approximately the first 6 months, prophylactic use of anti-inflammatory therapy (eg, colchicine or a nonsteroidal anti-inflammatory drug) is recommended during that time frame.¹³

Allopurinol

In patients with normal kidney function, allopurinol is initi-

ated at a low dosage (100 mg/d) and increased by 100 mg/d increments every 2 to 4 weeks if required, to reach the uricemic target.¹² A reduced initial dose, eg, 50 mg/d, and a daily dose of 200 mg is suggested in patients with a creatinine clearance of 10 to 20 mL/minute. This approach can minimize the risk of a severe cutaneous hypersensitivity reaction (eg, Stevens-Johnson syndrome) as well as an acute gout flare.¹² In approximately 30% to 50% of patients with normal kidney function, 300 mg/d is the most commonly used dosage of allopurinol. Because 300 mg/d does not achieve the target sUA level of <6 mg/dL in more than 50% of patients with gout, guidelines recommend dosage escalation when needed to reach the sUA target.¹⁵ Dosages of 600 to 800 mg/d have a 75% to 80% success rate in achieving an sUA level <6 mg/dL.¹² Dosages >300 mg/d are given in divided doses to avoid gastrointestinal side effects. In patients with renal impairment, EULAR guidelines recommend adjusting the allopurinol dosage downward due to the risk of serious cutaneous adverse events.¹² ACR guidelines, however, recommend increasing allopurinol until the sUA target level is reached in these patients, while monitoring for drug toxicity.¹⁵ The ACR recommendation is based on several small series of patients in which no increased incidence of severe reactions was demonstrated in patients whose allopurinol dosages were progressively titrated above those recommended, based on creatinine clearance and the level of renal impairment.^{6,18,19,26-28}

Febuxostat

Febuxostat is approved by the FDA at a starting dosage of 40 mg/d, uptitrated to 80 mg/d if patients do not achieve an sUA level <6 mg/dL after 2 weeks.²⁰ ACR guidelines suggest uptitration to as much as 120 mg/d (an investigational dosage) if necessary to achieve the target sUA level.¹⁵

Probenecid

The initial dosage of probenecid is 250 mg twice daily, uptitrated weekly to 1 g twice daily, based on the sUA level.⁶ Patients must be counseled to hydrate well due to the risk of urolithiasis.¹⁵ Probenecid is not recommended for patients with a creatinine clearance <50 mL/min, due to lack of data on long-term safety and efficacy in stage 3 CKD.¹⁵

Lesinurad

Lesinurad is indicated at a dosage of 200 mg/d as add-on therapy to allopurinol or febuxostat.¹⁶ Lesinurad should not be initiated in patients with a creatinine clearance <45 mL/min; renal function should be evaluated prior to initiation and periodically thereafter.¹⁶ Lesinurad is available as a 200 mg tablet and as a combination tablet of

200 mg of lesinurad with either 200 mg or 300 mg of allopurinol, which may improve patient adherence and lessen the risk of lesinurad being inadvertently taken without allopurinol.^{16,29}

Pegloticase

Pegloticase must be administered under supervision at an infusion center, due to the high risk of serious allergic reaction, including anaphylaxis.³⁰ Pegloticase is administered as an 8-mg IV infusion every 2 weeks, and should not be combined with other urate-lowering medications.³⁰

CASE STUDY, HARRIET (CONTINUED)

Because Harriet has not reached the sUA target of <6.0 mg/dL and she is tolerating allopurinol, the decision is made to increase the dosage of allopurinol to 200 mg twice daily and recheck the sUA level in 2 weeks.

SUMMARY

Gout is a common disorder that is associated with significant patient morbidity, as well as with comorbidities such as CKD, diabetes, and various cardiovascular disorders. Diagnosis is often based on history and physical examination, with confirmation by joint aspiration when necessary. Lifestyle management generally provides modest reduction of the sUA level. Several urate-lowering medications have been approved for chronic therapy. Allopurinol is typically used as first-line therapy. When combination therapy is required to achieve the target sUA level, the choice is generally based on patient-specific factors, physician and patient choice, and cost. ●

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