Limitations of the Current Standards of Care for Treating Gout and Crystal Deposition in the Primary Care Setting: A Review

Robert T. Keenan, MD, MPH

Department of Medicine, Division of Rheumatology and Immunology, Duke University School of Medicine, Durham, North Carolina

ABSTRACT

Purpose: This article outlines several important issues regarding the management of patients with gout. The topics discussed include best practices for gout based on the most current guidelines, opportunities for improving gout management, and current and emerging therapies for gout.

Methods: [PubMed and Google Scholar databases] were search for all articles and trials published before 2016, using the key terms [hyperuricemia, gout, tophi, joint erosion, joint damage, treatment guidelines, American College of Rheumatology (ACR), European League Against Rheumatism (EULAR), flare, comorbidity, epidemiology, adherence, serum uric acid (sUA), monosodium urate (MSU), <6 mg/dL, MSU crystal formation, as well as individual drug names and classes of treatments of interest (allopurinol, febuxostat, colchicine, non-steroidal anti-inflammatories (NSAIDs)]. Studies were selected that presented data on gout treatment, including drugs under development, and on the management of gout from both the physician and patient perspectives. The reference lists of identified articles were searched manually for additional publications.

Findings: Gout, a progressive debilitating form of inflammatory arthritis, is caused by factors that elevate serum uric acid (sUA) levels, leading to hyperuricemia. Continued elevated sUA can result in monosodium urate crystal deposition in joints and soft tissues, causing acute and chronic inflammation. Crystal deposition can lead to chronic gout, with an increased number of flares, tophi development, and structural joint damage. The aims of gout treatment are to reduce the sUA level to <6 mg/dL, to inhibit the formation of new crystals, and to promote the dissolution of existing crystals. Gout is often poorly managed for several reasons, including a lack of adherence to treatment guidelines by health care providers, patients’ poor adherence to therapy, and differences between a provider’s and patient’s perspectives regarding treatment.

Implications: Patients need to be educated about their diagnosis and management of the disease, such as the importance of compliance with long-term treatment. Gout treatment may also be confounded by contraindications to current standards of therapy and the limitations of current treatment paradigms. Recently approved medications, as well as drugs under development, may provide new ways for reaching the sUA target and also “curing” the disease. (Clin Ther. 2016;38(3) © 2016 The Authors. Published by Elsevier HS Journals, Inc.

Key words: gout, hyperuricemia, serum uric acid, treatment, uricosuric drugs, xanthine oxidase inhibitors.

INTRODUCTION

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MATERIALS AND METHODS

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RESULTS
Background and Epidemiology
Gout is the most common inflammatory arthritis in the United States, affecting 8.3 million adults (~4%), while hyperuricemia, the root cause of gout, affects 43.3 million (~21%).1,2 The prevalence of gout in the United States increased 2-fold between the 1960s and the 1990s, with further increases anticipated over the next several decades.1 Considering this increase, and the multiple comorbid conditions associated with gout, it may be of no surprise that there has been a rise in the costs of care of patients with gouty arthritis. During 2005 to 2011, the estimated costs of all-cause gout, which include the costs of emergency department visits, ambulatory care visits, inpatient stays, prescription medications, and other costs (eg, home health care), was $31.8 billion.3 In 2008, gout was the reason for ~175,000 emergency department visits, accounting for ~0.2% of all visits that year, and in 2002 gout was associated with 3.9 million ambulatory care visits, ~40% of cases of which were treated by primary care providers (PCPs).4 Gout can have a significant impact on a person’s life, and refractory gout, in which signs and symptoms are poorly controlled, is associated with a significant loss of the ability to perform daily activities, a loss of work productivity, and a low health-related quality of life.5,6

Gout is characterized by the deposition of monosodium urate (MSU) crystals resulting from hyperuricemia, defined as a serum uric acid (sUA)
concentration that exceeds the point of physiologic saturation of sUA (6.8 mg/dL in vitro, at 37°C and pH 7.4). Hyperuricemia is the greatest risk factor for the development and prevalence of gout, which results from the crystallization, deposition, and aggregation of MSU crystals in the joints and soft tissue, such as the kidneys (Figure 1). Once crystal deposition occurs, an inflammatory response ensues, causing low-level or subclinical inflammation resulting in bone erosion and soft tissue destruction. Before the development of clinically evident tophi, this ongoing crystal deposition may be apparent only with advanced imaging techniques, such as dual-energy computed tomography, computed tomography, or ultrasonography (Figure 2). The episodic nature of acute flares can be misleading because continuing damage, due to persistent MSU crystal deposition and inflammation, can occur during intercritical (asymptomatic) periods. Chronic gout typically develops after years of acute episodic gout, and is indicated by a loss of intermittent pain-free periods. Only ~22% of patients with asymptomatic hyperuricemia develop gout, depending on age, dietary tendencies, and the presence of comorbid conditions, such as renal insufficiency, congestive heart failure, hyperinsulinemia, and obesity. In boys, hyperuricemia can begin just after puberty, and in healthy women, it usually does not develop until menopause, indicating the role that the sex hormones play in urate regulation. Additionally, certain medications and even osteoarthritis and joint damage may play active roles in the promotion of hyperuricemia and the development of gout.

Urate levels are in part, determined by how much the body produces and how much it is able to eliminate, with decreased renal excretion being the primary cause of increased sUA levels in ~90% of people (Figure 3). In a healthy person, ~10% of uric acid filtered by the glomerulus is excreted in the urine. The rest is reabsorbed via organic anion transporters, such as urate transporter (URAT)-1, organic anion transporters 4 and 10, and glucose transporter 9. The most important of the transporters with respect to urate levels is URAT1.

Current Clinical Targets as per Clinical Practice Guidelines on Gout Management

Crystal formation is reversible, which means that gout can be “cured.” The crystals will dissolve when sUA levels drop to below the limit of solubility (ie, 6.8 mg/dL). The lower the sUA level, the faster the crystal deposition (and tophi) will resolve. Therefore, the goal of therapy is to lower the sUA level to below the limit of solubility (sometimes well below). The American College of Rheumatology (ACR) and the European League Against Rheumatism recommend a minimum sUA target of <6 mg/dL and a lower target (<5 mg/dL) to improve gout signs and symptoms in patients with more severe disease. The British Society of Rheumatology recommends a target of <5 mg/dL in all patients with gout.

Gout treatment should improve disease outcomes by eliminating gout flares, by inducing long-term
Establish diagnosis of gout

Baseline recommendations for patients diagnosed with gout
- Patient education, with initiation of diet, lifestyle recommendations
- Consider secondary causes of hyperuricemia (eg, comorbidities)
- Consider elimination of non-essential prescription medications that induce hyperuricemia
- Clinically evaluate gout disease burden (palpable tophi, frequency and severity of acute and chronic gout symptoms)

Assess whether pharmacologic urate-lowering therapy is necessary
- Presence of tophus or tophi
- Frequent flares
- Stage 2 or greater kidney disease
- Past urolithiasis

If pharmacologic urate-lowering therapy is necessary TREAT TO SERUM URATE TARGET (<6 mg/dL)
- Select first-line therapy: xanthine oxidase inhibitors (allopurinol or febuxostat) if xanthine oxidase inhibitors contraindicated or not tolerated, alternative first line: probenecid
- Acute gout prophylaxis: initiate concurrent pharmacologic anti-inflammatory gout attack prophylaxis

Once achieved TARGET (6 mg/dL) - long-term management of gout
- Continue gout attack prophylaxis
- Continue to regularly monitor serum urate even after palpable tophi and all acute and chronic gout symptoms have resolved
- If necessary, refer patient to a specialist (unclear hyperuricemia etiology, refractory signs and symptoms, difficulty in reaching target serum urate levels, multiple or severe adverse events for pharmacologic treatment

Interventions targeting adherence
- Patient education & self-management training
- Medication titration

Patient factors
Barriers
- Younger age
- Fewer comorbidities
- Ethnic populations
- Concerns about ULT effectiveness, side effects, polypharmacy
Facilitators
- Pain and prevention of flares
- Medication as part of daily routine

Physician factors
Barriers
- Low rates of ULT prescription
- Failure to co-prescribe prophylactic when initiating ULT
- Minimal referral to specialists for gout management

Medication adherence
Recent estimates: 40% to 83%

Healthy System factors
Barriers
- Prescription costs

Figure 4. Gout treatment and treatment barriers. A, American College of Rheumatology treatment algorithm for gout. Adapted with permission.23 B, Barriers to long-term gout treatment adherence. ULT = urate-lowering therapy. Adapted with permission.33.
resolution of tophi, and by effectively managing comorbidities, many of which promote hyperuricemia. The ACR recommends both nonpharmacologic and pharmacologic approaches to treating the disease (Figure 4A). Nonpharmacologic approaches include educating patients about lifestyle changes that reduce the risk for flares, such as losing weight and avoiding "trigger" foods that are rich in purines (eg, beer, shrimp, red meat). Patients need education about treatment objectives and about the management of comorbidities, and should discontinue nonessential prescription drugs that elevate sUA (Table). Following nonpharmacologic approaches, the ACR recommends an evaluation for the use of urate-lowering therapy (ULT), which may be appropriate in patients with the following: tophus or tophi (verified by clinical examination or imaging study), ≥2 gout flares per year, stage ≥2 chronic kidney disease, and/or previous urolithiasis. An individual’s risk for further gouty attacks, existing damage from tophi and/or associated disability, medication/treatment preference, and relative risks of available treatments should also be considered.

First-line therapy involves xanthine oxidase inhibitors (XOIs; eg, allopurinol or febuxostat), or, if necessary due to poor tolerability or contraindications, alternative therapy (eg, probenecid). If an sUA level of <6 mg/dL is not achieved with an XOI, the ULT dose can be increased, or a uricosuric, such as probenecid, may be added. Pegloticase can be considered for severe or refractory disease or in patients who are intolerant to appropriately dosed oral therapy. When ULT is started, prophylaxis treatment, which may include NSAIDs and low-dose colchicine, should also be initiated to reduce the increased risk for acute gouty attacks during the early phase of treatment. If a patient cannot take one of these drugs (eg, due to a contraindication), or if a patient is not responding to flare prevention, then a low-dose glucocorticoid can be used instead. Once the target of <6 mg/dL is achieved, long-term maintenance ULT is prescribed to keep the sUA level <6 mg/dL, and flare prophylaxis treatment should continue for at least 6 months, or 6 months after the last flare, whichever is longer. sUA levels should be

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<td>Secondary gout</td>
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<td>Drugs</td>
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<td>Excessive urate production</td>
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<td>Pancreatic extract</td>
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<td>Cytotoxic drugs</td>
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<td>Red meat, organ meat, shellfish</td>
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<td>Alcoholic beverages (especially beer)</td>
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<td>Fructose</td>
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GFR = glomerular filtration rate; HPRT = hypoxanthine-guanine phosphoribosyltransferase; PRPP = phosphoribosyl pyrophosphate.
Adapted with permission.18
monitored every 2 to 5 weeks (in addition to liver function testing, creatinine measurement, and complete blood counts) while the ULT dose is titrated. After the target sUA has been reached and no ULT dose adjustments are needed, laboratory monitoring can be performed every 6 months.

Health care providers may also consider treatment in patients who might not meet all of the criteria for ULT as defined in the guidelines. For example, a patient who experiences flares only once per year, but who has an sUA level of >9.0 mg/dL, may benefit from ULT because increased flares and disability are more likely over time. In addition, some patients with chronic or recurrent gout plus other conditions will require tailored management requiring a specialist, such as elderly patients (>75 years of age, multiple comorbid conditions, on CYP3A4 inhibitors) and those with renal insufficiency, underlying myeloproliferative disease, or rare inherited disorders.25

Maintaining a level of sUA <6 mg/dL can help reduce the occurrence of flares, inhibit further MSU crystal deposition, prevent tophi formation, and accelerate dissolution of tophi.8 It also can alter progression of radiographic changes and possibly improve bone erosions, but not structural changes to cartilage.29

**Barriers to Treatment Success and Unmet Needs for Better Treatment Options**

Although effective treatment options for gout are available and the disease is well understood, gout is often poorly managed.10 For example, in a study in 400 patients treated with allopurinol for symptomatic gout, 36% had a urate level of ≥6 mg/dL at screening and required a dose increase.30 A recent 12-month retrospective study of data from the clinics of 124 PCPs and 125 rheumatologists managing >1200 patients over the course of 12 months found that disease control, defined as an sUA of <6 mg/dL, no flares, and no tophi, was achieved in only 11% of patients.31 In a 6-month, multicenter, open-label, uncontrolled observational study in patients with gout that allowed for a titration of allopurinol from <300 to >300 mg/d, a target sUA of <6.0 mg/dL was achieved in 35.9% of patients.32 The study revealed that an obstacle to treating to target was underdosing of allopurinol.32

**Patients’ Treatment Adherence**

There are several challenges with regard to treating and managing gout (Figure 4B).15,33 Studies have shown that patients and providers are both involved in suboptimal outcomes. Two retrospective studies found that ~14% to 56% of patients who were started on ULT were nonadherent, particularly those who were younger (<45 years of age), had fewer comorbidities, and/or had not visited a health care provider before the gout developed.34,35 A systematic review of data from electronic prescription records across 10 studies found that adherence rates ranged from 10% to 46%, which is below the World Health Organization’s estimate that 50% of adults adhere to long-term therapy across the chronic disease spectrum.36,37 However, increased adherence rates were associated with older age and comorbid hypertension.36 Further reasons for poor adherence included a lack of education and understanding about how to take the medication, and about how the medication fits into disease management. Additional reasons for poor adherence included the lack of financial resources and the lack of self-motivation for taking medication regularly.33,38 Other barriers to patients’ gout management are the feeling/belief that a drug is ineffective, confusion about whether ULT is for acute flares versus chronic prophylaxis of flares, copayment costs, adverse events with medication use, and concerns regarding taking multiple medications on the same day.33 One US study found that patients had a lack of awareness about the duration of therapy, about the role of allopurinol in treatment (prevention vs pain relief), and/or about what triggers a gout flare, and that they were unhappy with the information provided by their health care professionals.39 Another US study found that patients also had a poor understanding about dietary triggers and about the need for long-term use of medications.38 These studies illustrate the need for better patient education about gout management and its short- and long-term implications.

**Health Care Providers’ Adherence to Clinical Practice Guidelines**

Rheumatologists and PCPs have less-than-optimal overall adherence to treatment guidelines, particularly with regard to first-line ULT and duration of prophylactic treatment.40,41 For example, a comprehensive quantitative US survey that assessed PCPs’ (n = 120)
and rheumatologists’ (n = 71) adherence to the ACR guidelines found that 53.7% of PCPs and 35.3% of rheumatologists had low adherence, defined as following ≤4 of the 8 ACR treatment recommendations, and only 36.4% and 35.2%, respectively, prescribed the recommended initial ULT dose.40 Another study showed that only ~50% of patients with acute gout flares received treatment that was consistent with the guideline recommendations, and <20% of patients with intercritical (the time between acute flares) and tophaceous gout were managed according to guidelines.41 Prophylaxis to prevent acute attacks in patients with tophaceous gout before or at the time of ULT initiation was implemented in only ~17% of cases. The lack of compliance with guidelines was largely accounted for by inappropriate dosing of medications in the setting of renal disease and by a lack of prophylaxis when initiating ULT.41 There was also poor compliance with the recommendations of patient education and lifestyle counseling.41 The same study reported that only a quarter to a third of PCPs monitored sUA levels as recommended by the guidelines, raising questions about whether providers are treating to the sUA target of <6 mg/dL.41 The appropriate medication was not being prescribed in patients who were candidates for ULT, resulting in preventable gouty flares with associated morbidity and hospitalizations.41 The suboptimal treatment of gout may in part reflect a poor understanding of hyperuricemia and gout on the part of health care providers, due to infrequent medical education, insufficient evidence-based medicine, and, for those in busy practices, a lack of motivation to relearn the disease.42 Additional challenges occur with the presence of comorbidities and drug–drug interactions. One study found that, in a cohort of patients meeting the ACR’s criteria for gout (N = 575), >90% had at least 1 contraindication to NSAIDs; 43%, to allopurinol; ~50%, to colchicine; and 94.4%, to glucocorticoids.43

**Patient–Provider Discordance Regarding Perceptions about the Disease and Its Treatment**

Differences between health care providers and patients with regard to perceptions about gout and its treatment can also influence care. One study from the United States examined patients’ and providers’ views on the treatment of gout to provide insight into why gout management is suboptimal.39 The investigators found that health care providers thought that the majority of patients had excellent relief with NSAIDs, colchicine, and/or glucocorticoids, although some patients believed that the medications were ineffective.35 In addition, most providers thought that patients had a good understanding of the rationale for ULT and that patients responded well to treatment, whereas patients believed that ULT worsened, triggered, or had no impact on their disease.39 Most providers also believed that therapy adherence was good; however, a number of patients discontinued their medication due to financial and/or clinical concerns, such as the belief that treatment worsened the disease or that medications were ineffective.39 Providers believed that they adequately educated their patients about disease management, whereas most patients indicated that they had requested additional information. Finally, most providers were not aware of the difficulties that patients have with gout treatment, such as financial concerns, adverse events with medication use, inadequate symptom relief, and a lack of information from their health care providers.39

**Current Treatment Options**

Currently, ULT options are limited and may be contraindicated in many patients with gout. It is common for gout flares to occur on initiation of ULT or when a dose is increased, thus the ACR’s guidelines recommend concurrent anti-inflammatory prophylaxis for a minimum of 6 months.33,44 Colchicine and NSAIDs are first-line prophylactic anti-inflammatory treatment, and low-dose prednisolone is second line.45 An interleukin-1 blocker may be used in patients with frequent flares and contraindications to colchicine, NSAIDs, and/or corticosteroids. The anti–interleukin-1β monoclonal antibody canakinumab has been approved for this indication in Europe46; however, it has not been approved by the US Food and Drug Administration.

Although >90% of hyperuricemia is due to renal underexcretion,18 the first-line ULTs, allopurinol and febuxostat, address uric acid production. The ACR recommends a 100-mg/d starting dose of allopurinol, with gradual up-titration every 2 to 4 weeks until the target serum urate level is achieved.23 In patients with chronic kidney disease, treatment should be started at a low dosage (50 mg/d) and increased more slowly than in patients without renal function impairment.23
Historically, patients with chronic kidney disease were considered to be at greater risk for toxicity with allopurinol use because oxypurinol, a metabolic product of allopurinol, is cleared by the kidney.47 However, a recent study found that allopurinol was not associated with an increased risk for renal function deterioration in patients with gout.48 A study by Stamp et al49 found that a high starting dose of allopurinol rather than the maximum dose, regardless of renal function, was a risk factor for allopurinol hypersensitivity syndrome, which is rare but has been associated with a mortality rate of 27%.50 Patients of Han Chinese and other Asian descent and having the HLA-B*5801 genotype have an increased risk for allopurinol hypersensitivity syndrome and should be screened for the allele prior to initiating allopurinol treatment.23,24 A number of other adverse events, such as nausea or vomiting, rash, and Stevens-Johnson syndrome, have also been associated with allopurinol use.50

Febuxostat, in contrast to allopurinol, is not a purine analogue. The recommended starting dosage is 40 mg once daily.51 In patients who do not achieve an sUA of <6 mg/dL after 2 weeks at 40 mg, 80 mg/d is recommended.52 Febuxostat is eliminated by both the hepatic and renal pathways, and no dose adjustments are needed in patients with mild to moderate hepatic or renal impairment. It has been associated with limited drug interactions, but with a statistically nonsignificant increase in cardiovascular events.44,50

Uricosuric agents such as probenecid, sulfinpyrazone, and benzbromarone were introduced for the treatment of gout before the availability of allopurinol. Benz bromarone was withdrawn from the US market by the original manufacturer due to potential hepatotoxicity, and the availability of sulfinpyrazone worldwide is limited. As a result, probenecid is the only uricosuric readily available in the United States; however, probenecid has been associated with drug–drug interactions, some of which are related to its ability to block the renal tubular transport of acidic drugs.53 Despite its declining use in the United States and abroad, probenecid is still used by some patients with gout. Caution is required when prescribing uricosurics in patients with a history of kidney stones, as uricosurics can precipitate uric acid stones.44

In 2010, the US Food and Drug Administration approved the use of pegloticase. Unlike other ULTs that either block the production or increase the excretion of uric acid, pegloticase is unique in that it provides the absent enzyme, uricase, that catalyzes the oxidation of uric acid into allantoin, which is more soluble than uric acid and allows for easier excretion by the kidney. The oxidative products of hydrogen peroxide and carbon dioxide are the byproducts of this lost conversion process in humans and primates.53 Due to the rapid urate reduction with pegloticase, its use has been associated with a significant prevalence of acute flares even in the presence of prophylactic treatment.54 In studies, infusion reaction–related adverse events occurred in about 26% to 41% of patients and included flushing, chest discomfort, and dyspnea.55,56 Infusion reactions were particularly more common in patients in whom a high level of antipegloticase antibodies developed.53

Treatment guidelines recommend combination therapy (uricosuric plus an XOI) when treatment goals are not achieved with single-agent XOI, or pegloticase for severe, refractory chronic gout.23 Using drug combinations that reduce uric acid production and increase renal excretion target the 2 etiologies of the disease, which may more effectively reduce the concentration of sUA to <6 mg/dL.57 Pegloticase may be a viable option in cases in which the target sUA is not reached or gouty arthritis and disability persist.23

New Treatment Options

A number of new uricosuric agents that may be more efficacious in reducing sUA levels are being developed for treating gout.58 Lesinurad was recently approved by the US Food and Drug Administration for use as an adjunct therapy with an XOI. Lesinurad works by inhibiting URAT1 in the kidney, thereby increasing uric acid secretion.58,59 The prevalence of renal related adverse events, including those resolved, occurred in 5.9% of lesinurad 200 mg + allopurinol and 4.9% of allopurinol-alone groups. In the lesinurad 400 mg + allopurinol group, 15.0% had either a permanent or temporary increase in serum creatinine.60 Lesinurad 200 mg with a xanthine oxidase inhibitor was approved by the FDA, while the 400 mg dose was not. Lesinurad has been associated with adverse events related to renal function, including transient elevations in creatinine and kidney stones. In clinical studies, an elevation of serum creatinine to 2-fold above baseline level was
observed in some patients, but most cases resolved without treatment adjustment. Lesinurad use is contraindicated in patients with severe renal impairment (estimated creatinine clearance <30 mL/min), tumor lysis syndrome, or Lesch-Nyhan syndrome. Other common adverse events included headache, influenza, and gastroesophageal reflux disease. Arhalofenate is in Phase III clinical development for use in fixed-dose combination with febuxostat as a once-daily, oral gout treatment. Arhalofenate has dual mechanisms of action that lower sUA levels by inhibiting URAT1 and decrease in inflammation by limiting interleukin-1β production. RDEA3170 is a URAT1 inhibitor in Phase II clinical development for use as monotherapy or in combination with febuxostat. URC102 is another URAT1 inhibitor in Phase II clinical development in Korea.

CONCLUSIONS
Gout is the most common inflammatory arthritis in the United States, causing significant disability and morbidity, and is characterized by underlying hyperuricemia, MSU crystal deposition, and recurrent flares. Even when patients are asymptomatic and free of flares, in the setting of crystal deposition, ongoing inflammation and subsequent damage occur in the joints and soft tissues. The ACR and the European League Against Rheumatism guidelines recommend a target sUA level of <6 mg/dL to prevent the formation of MSU crystals and to eliminate crystal deposition, thereby dissolving tophi. In addition, they recommend pharmacologic and nonpharmacologic (ie, education, lifestyle counseling) interventions to treat and manage the disease.

Despite the increased dialogue regarding gout over the past several years, many patients continue to receive suboptimal care due to a number of factors, including patients' treatment nonadherence, health care providers’ lack of adherence to treatment guidelines, and differences in patients’ and providers’ perspectives on the treatment of gout. To improve care, there is a need for ensuring proper dosing of prescribed medications and treatment compliance, and for increasing education of both patients and health care providers regarding the disease, its treatment, and the importance of achieving the goal of an sUA level <6 mg/dL. Treatment may also be improved by including the topic of gout in provider–patient discussions about chronic disease and comorbidities, by providing patient education, by regularly monitoring adherence, and by attaining patients’ participation in their treatment plans to facilitate adherence.

The treatment of gout is confounded in patients with multiple comorbidities and/or contraindications to current therapies, and by current treatment paradigms that fail to address the etiology of hyperuricemia in the vast majority of patients. The use of lesinurad has recently been approved, and additional new uricosuric drugs are being developed, for use in combination with an XOI for the long-term management of gout. These treatments are expected to provide additional options for reaching not only the sUA target but also the clinical target of "curing" these patients of the disease.

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Address correspondence to: Robert T. Keenan, MD, MPH, Division of Rheumatology and Immunology, Duke University Hospital, 4022 Hospital South, Box 3544, Durham, NC 27710. E-mail: robert.keenan@duke.edu