Management and Cure of Gouty Arthritis

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KEYWORDS

• Gout • Inflammatory arthritis • Uric acid • Hyperuricemia • Treat-to-target

KEY POINTS

- Gout is a disease of urate deposition; flares represent symptoms of the disease.
- To stop gout flares, urate deposits must be eliminated with persistent maintenance of low serum urate below the saturation point. A reasonable target is 6.0 mg/dL or less.
- Flare prophylaxis—typically with colchicine or low-dose nonsteroidal anti-inflammatories—must be initiated along with urate-lowering therapy.
- Do not stop urate-lowering therapy during gout flares or when the patient is admitted to the hospital unless there is a need for strict no oral intake.
- Treat gout flares until symptoms are completely resolved before tapering or stopping the anti-inflammatory treatment. Be aware of comorbidities and optimize treatment of these conditions.

INTRODUCTION

With a prevalence of 3.9% among all adults, and 9.7% in those older than 80, gout is the most common inflammatory arthritis.[1] An analysis of National Health and Nutrition Examination Survey data determined that two-thirds of patients diagnosed with gout do not receive urate-lowering therapy.[1] Because urate-lowering therapy is the only method by which gouty arthritis can be cured, a treat-to-target strategy of lowering serum urate must be widely adopted by primary care providers to optimize care of patients with gout.

GOUT DIAGNOSIS

The gold standard for the diagnosis of gout is the demonstration of monosodium urate (MSU) crystals in synovial fluid or documentation of tophi. Documenting the presence of MSU crystals in the body fluid or tissue is sufficient to diagnose gout. However, because acute gout can occur coincidentally with other types of arthritis, the

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demonstration of MSU crystals confirms gouty arthritis but does not rule out a concomitant septic joint, acute calcium pyrophosphate arthritis (pseudogout), or another inflammatory arthritis such as psoriatic, which can also present acutely in 1 or a few asymmetric joints. Nonetheless, it is recognized that arthrocentesis and crystal analysis is not always an option.

NONINVASIVE DIAGNOSIS BY CLINICAL ALGORITHM

The diagnosis of gout may be reasonably presumed when joint fluid cannot be obtained based on the patient's historical and clinical features or on imaging results. It should be noted (and recorded in the medical record) that without direct documentation of the presence of MSU crystals, the diagnosis is best considered as presumptive.

Several clinical algorithms have been developed to assist in gout diagnosis. One diagnostic tool was developed and validated among 328 Dutch patients.[2] Using this algorithm, the probability of gout is graded as low, intermediate, or high based on 7 weighted variables (male sex, previous patient-reported arthritis flare, onset acutely within 1 day, presence of joint redness, first metatarsal phalangeal joint involvement, hypertension or at least 1 cardiovascular disease (CVD), and a serum urate level of >5.88 mg/dL). Additional diagnostic studies (such as joint aspiration or imaging studies) should be used for those patients who fall into the intermediate category or if patients do not follow the expected clinical course. The take home message supporting the use of such algorithms is that there are characteristic features of gouty arthritis, but they are not 100% specific, which is important to remember when prescribing patients lifelong drug therapy and when assuming that an acutely inflamed joint is not infected.

NONINVASIVE DIAGNOSIS BY IMAGING

The diagnosis of probable gout can be supported by the demonstration of characteristic findings on plain radiographs, musculoskeletal ultrasound (US) examination, computed tomography (CT) scan, and dual energy CT (DECT) scan. Plain radiographs can be useful in identifying the very late changes of longstanding gout. Gouty erosions tend to be periarticular lesions with sharp, sclerotic margins, which are asymmetric in distribution.[3] These erosions appear as "punched out" of the cortex with pathognomonic "overhanging edges" and a "rat bite" appearance.[4] In contrast with the lesions seen in rheumatoid arthritis, mineralization of the bone and the joint space are typically both preserved in gouty arthritis.[3] Tophaceous depositions of MSU crystals are not themselves radiographically opaque; calcification within the tophus and soft tissue swelling can be evident on a radiograph and support the diagnosis of probable gout.[4] Standard radiography is not a useful diagnostic tool in new cases.[5]

Musculoskeletal US examination, CT scan, and DECT scan have significantly advanced our ability to diagnose probable gout noninvasively because these modalities have an increased sensitivity to detect features of urate deposition. Musculoskeletal US imaging can be used at the point of care in the rheumatology clinic. Well-established US features of an acute gout flare include occasionally visualizing free MSU crystals within the joint ("snowstorm" appearance) as well as synovial hypertrophy and hypervascularity (as seen by color power Doppler imaging).[5] Deposition of urate can be demonstrated by the "double contour sign," a layer of crystals overlying hyaline articular cartilage.[5] This appearance differs from the intracartilage deposition of calcium pyrophosphate. Gouty erosions and tophi can also be visualized by US imaging. These findings can strongly support the diagnosis of probable gout, but the technique is operator dependent.

CT scan is an effective modality to image bony deformities, such as erosions and calcified tophi, because these changes can be accurately demonstrated and differentiated from soft tissues based on Hounsfield units.[6] A DECT scan uses 2 different x-ray energies to identify the chemical structure of a given substance based on differences in energy attenuation.[3] In this case, MSU crystals are identified in musculoskeletal structures (eg, joints, tendons, ligaments, muscles) and depicted as a specific color using postprocessing software. As a result, a DECT scan can be used as a method for diagnosing probable gout in the appropriate clinical context. However, although specificity of this modality is high, sensitivity is less than ideal in both acute and tophaceous gout, but it may demonstrate urate deposits in periarticular areas that otherwise might not be detected.[7] Notably, MRI may not reliably distinguish tophus from soft tissue infection.

Although noninvasive approaches can be used when needed, visual crystal documentation remains the gold standard and should be attempted when possible. Synovial fluid analysis with culture should be performed if there is any clinical suspicion for infection.

THERAPEUTIC OPTIONS: TREATMENT OF ACUTE FLARES

Acute flares must be treated while working toward dissolution of urate deposits and cure of gouty arthritis. Nonsteroidal anti-inflammatory drugs (NSAIDs), oral colchicine, glucocorticoids (oral, intramuscular, intra-articular, or intravenous), and IL-1 inhibitors can effectively treat gout flares. A critical concept is that flares are a symptom of the underlying disease, namely, the deposition of urate.

According to current society guidelines, NSAIDs, oral colchicine, and glucocorticoids are considered first-line therapies for the treatment of an acute gout attack. IL-1–directed therapy (off label in the United States) should be considered if there are contraindications to the first-line therapies, or if a patient cannot tolerate or does not respond to the therapies described.[8,9] Choice of agent depends on the patient's preference, response to treatment in the past, and the presence of comorbidities.

Colchicine and NSAIDs are effective, readily available, and reasonably well-tolerated. These medications have historically been said to be most effective when initiated within the first 24 to 48 hours of a flare. A potent, generic nonselective cyclo-oxygenase inhibitor such as naproxen or indomethacin is often prescribed at high doses.[10] An open-label randomized trial comparing naproxen with low-dose colchicine in the primary care setting found that there was no difference in treating pain between these 2 medications, although naproxen caused fewer side effects.[11] Selective cyclo-oxygenase-2 inhibitors (such as celecoxib) can be used if there is need to avoid an antiplatelet effect, but higher than the usually prescribed dose may be required.[12] NSAIDs present a therapeutic challenge because many patients with gout have comorbidities that preclude their safe use.[13] Proton pump inhibitors should be considered as gastroprotection.[9]

Colchicine can be effective in the treatment of an acute flare, particularly if initiated early during the course of the flare, or if the attack is mild. The trial-based initial dose of colchicine is 1.2 mg followed by 0.6 mg 1 hour later in patients with normal renal function. High-dose oral colchicine (0.6 hourly over 6 hours) is not recommended because this dosing led to considerably more toxicity than the low-dose and provided no greater efficacy.[14,15] As is the case with NSAIDs, caution must be exercised in patients with chronic kidney disease (CKD) because colchicine is largely excreted by the kidney and is not dialyzable. Problematic is that, in the clinical trial demonstrating efficacy

in relief of pain, resolution of flare was not documented, and the majority of patients required "rescue" pain medication and continued therapy with colchicine.[14]

Chronically used colchicine must be dose reduced in patients with CKD and particularly those on hemodialysis, if used at all. Importantly, colchicine is metabolized by CYP3A4 and P-glycoprotein, leading to numerous drug–drug interactions.[16]

Glucocorticoids are often used if the patient has not responded to NSAIDs or colchicine, or if there are contraindications to these medications, particularly in the outpatient setting. Several randomized, controlled trials have established that glucocorticoids are as effective as NSAIDs for the treatment of acute gout,[17,18] and may have fewer short term side effects.[18] Prednisone or prednisolone can be used at a dose of 20 to 40 mg/d until inflammation has resolved, and then rapidly tapered over the course of 5 to 7 days. If a flare does not resolve with oral glucocorticoids, it is often because the dose was too low, or the therapy was tapered or stopped before complete resolution of flare. Intra-articular glucocorticoids can be considered if only 1 joint is affected and there is no significant concern regarding possible infection.

IL-1–directed therapy is increasingly used, particularly in the inpatient setting. MSU crystals, as well as calcium pyrophosphate dihydrate crystals, activate the NLRP3 inflammasome in mononuclear phagocytes.[15,19,20] This triggers an intracellular cascade of reactions that results in the release of proinflammatory cytokines, including IL-1β.[15,19,20] IL-1 has proven to be an effective target in treating acute gout. Agents that are directed against IL-1 include canakinumab (a human anti–IL-1β monoclonal antibody approved for treatment of gout in Europe) and the short-acting anakinra (recombinant IL-1 type 1 receptor antagonist). IL-1–directed therapy is well-tolerated with very few side effects. Indeed, this class of medication was initially developed to treat sepsis and is thought to be safe for patients in the critical care setting.[21]

Several observational and randomized controlled trials have demonstrated the efficacy of IL-1 inhibition in treating and preventing gout flares.[22] A randomized controlled trial investigating use of anakinra versus intramuscular methylprednisolone in patients with CKD is currently ongoing.[23] Currently, anakinra is the most commonly used treatment by our consult service as therapy for acute gout in hospitalized patients with significant comorbidities (usually some combination of heart failure, diabetes, and renal disease).

TREATMENT OF HYPERURICEMIA: ASYMPTOMATIC HYPERURICEMIA TO ADVANCED GOUT

The overall gout treatment strategy has numerous dimensions: treatment and prophylaxis of acute gout flares, initiation and escalation of urate-lowering therapy, and treatment of associated hyperuricemic–metabolic comorbidities.

In patients with asymptomatic hyperuricemia (>6.8 mg/dL), MSU crystals are potentially silently deposited in tissues in and around joints (such as tendons and bursae) as well as inside internal organs. Although there are known risk factors that may predispose a patient with asymptomatic hyperuricemia to develop gout, there is no way to determine with certainty which individual will develop gouty arthritis.[24] Surprisingly, some patients even with profound hyperuricemia (>10 mg/dL) will not develop gout even after 10 years. Treatment of asymptomatic hyperuricemia with urate-lowering therapy is thus not universally recommended, although it can be considered in certain circumstances.[8] The lifestyle and behavioral changes summarized in this article from the American College of Rheumatology guidelines are usually recommended for

patients with asymptomatic hyperuricemia as well as for all patients with gouty arthritis.[8] These recommendations include weight loss for patients who are overweight (diet, exercise, medications, bariatric surgery),[25] and modifying diet to limit intake of purine-rich foods,[26] limiting alcohol and nonalcoholic beers,[27] and limiting high-fructose containing beverages.[28] Last, the patient must be screened for the presence of components of the metabolic syndrome and coronary artery disease.

Flares occur when MSU crystals, presumably originating from tissue urate deposits, trigger an inflammatory response mediated by the NLRP3 inflammasome.[29] Once a gout flare occurs, there is a high likelihood that subsequent flares will recur in the future and will continue to increase in both severity and duration if urate-lowering therapy is not initiated.[24,30] In fact, approximately 90% of patients who experience 1 gout flare will have a subsequent flare at some point in their lifetime.[31] Thus, urate-lowering therapy should be considered. A slightly more conservative therapeutic approach, offered in the American College of Rheumatology gout guidelines, is to initiate urate-lowering therapy in patients who meet the following criteria: clinically or radiographically evident tophi or $\geq$ 2 flares per year. There is also a conditional recommendation to initiate urate-lowering therapy in patients with at least 1 flare, but less than 2 per year, and in patients with only 1 flare who have CKD $\geq$3, serum urate > 9 mg/dL or kidney stones.[8] We advocate for a more individualized approach. In certain circumstances, urate-lowering therapy should be strongly considered in patients who may not meet the American College of Rheumatology criteria but who would nonetheless benefit from earlier definitive treatment of the underlying disease process to prevent likely progression and put an earlier end to the risk for further gout flares. These patients can include transplant recipients, young patients with a family history of severe gouty arthritis, or those who experience debilitating, although infrequent, flares that negatively impact their quality of life or ability to perform their work.[31] **Box 1** and **Fig. 1** detail some situations in which urate-lowering therapy should be considered.

Acute flares are followed by periods of time when the disease may seem to be quiet clinically.[24] This intercritical period is misleading, because it is during this time that the patient and even the clinician may falsely believe that gout is no longer active. However, MSU crystals will continue to deposit in tissues, leading to the development of tophi and progression toward destructive arthritis while the threat of triggering a gout attack continues as long as there are urate deposits.[29] Urate-lowering therapy is crucial to prevent advanced gout, in which patients have chronic joint swelling and pain with potential for joint destruction.[24]

Box 1
When to initiate urate-lowering therapy

- Two or more flares per year
- Presence of tophi
- If fewer than 2 flares per year, urate-lowering therapy should be considered in an effort to stop future flares in the following cases:
  - Presence of kidney stones
  - CKD stage 3 or higher (as treatment of flares becomes more difficult)
  - Other conditions making the treatment of acute gout flares unsafe or difficult
  - Significant socioeconomic or medical challenges caused by gout attacks

Data from Pillinger MH, Mandell BF. Therapeutic approaches in the treatment of gout. Semin Arthritis Rheum 2020;50(3):S24-S30.

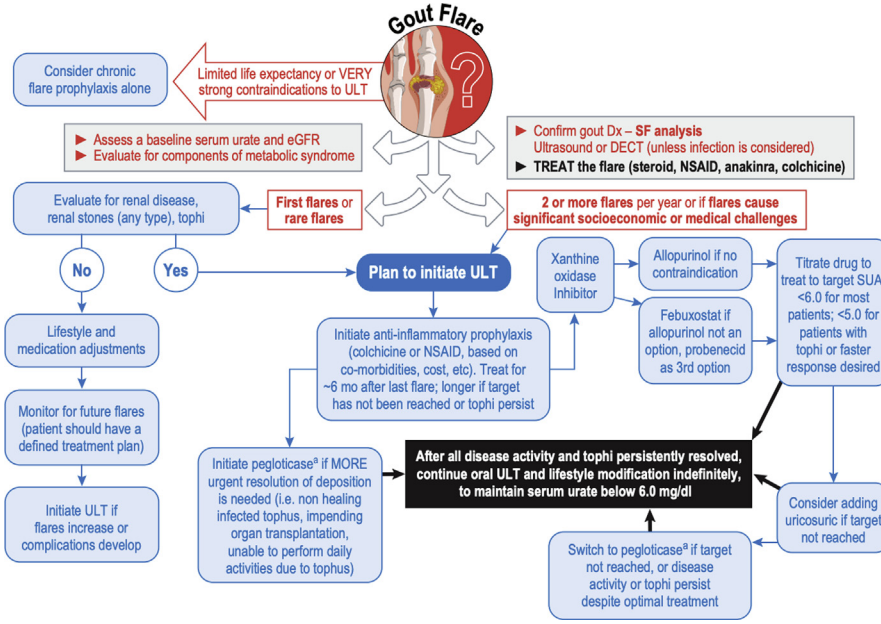

Fig. 1. Management of gout algorithm. DECT, dual energy computed tomography; SF, synovial fluid; SUA, serum urate level; ULT, urate-lowering therapy. [a] Do not use other urate-lowering therapy with pegloticase; monitor SUA before each infusion. (*From* Pillinger MH, Mandell BF. Therapeutic approaches in the treatment of gout. Semin Arthritis Rheum 2020;50(3):S26; with permission.)

ATTAINING CURE OF GOUTY ARTHRITIS: RATIONALE FOR TREAT-TO-TARGET THERAPY WITH URATE-LOWERING THERAPY

Gouty arthritis is the result of urate deposition from biologic hyperuricemia (>6.8 mg/dL). Because the total deposited urate cannot be readily measured, serum urate is used as a proxy therapeutic target. To cure gout, the serum urate must be targeted therapeutically and kept low enough to drive the dissolution of urate deposits by mass action effect down a concentration gradient. The lower the serum urate, the more rapid the resorption of deposits.

The saturation point of urate in serum is reached at approximately 6.8 mg/dL.[24] Any elevation above this solubility concentration will lead to supersaturation and the potential continued precipitation of MSU crystals out of serum and into soft tissue.[24,29] Of note, the upper limit of normal for serum urate as defined by the clinical laboratory is greater than 6.8 mg/dL, meaning that a patient who in fact has biologic hyperuricemia may be mistakenly considered as having a normal serum urate on population (not biologically) based laboratory values.[24] For this reason, serum urate should be lowered well below the solubility concentration. A commonly accepted therapeutic target for serum urate is less than 6.0 mg/dL for patients without tophaceous gout and less than 5.0 mg/dL for patients with clinically or radiographically evident tophi; the concept incorporated into several guidelines is that more extensive deposition represented by palpable tophi warrants more aggressive therapy with more rapid dissolution.

There is ample evidence, in the form of retrospective and prospective data, to support urate-lowering therapy in a treat-to-target approach. The optimal range of serum urate concentration to avoid gout flares was determined to be 4.6 to 6.6 mg/dL according to one analysis of retrospective data.[32] Another retrospective study demonstrated that reducing serum urate ultimately was associated with a significantly reduced risk of gout flares. Notably, among patients who had average serum urate concentration of less than 6 mg/dL, 86% (71 patients) did not have gout flares during the follow-up period of 3 years.[30] Prospective data regarding the benefits of extreme urate-lowering therapy are available from the 2 phase III randomized controlled trials that investigated the efficacy and tolerability of pegloticase. Among patients with an elevated serum urate, the use of pegloticase resulted in lower serum urate (primary study end point; often to levels $\leq$0.2 mg/dL), as well as a reduction in the proportion of patients with gout flare and nonstatistically significant decrease in the number of flares in the biweekly pegloticase group when compared with the placebo group during months 4 to 6 of the study.[33] Although no large randomized controlled trial was designed to evaluate the benefits of a treat-to-target approach to urate-lowering therapy, we believe that there are sufficient direct and indirect observational data to support the treat-to-target approach.

CONSIDERATIONS IN PATIENTS WITH ASYMPTOMATIC HYPERURICEMIA AND CHRONIC KIDNEY DISEASE

It has long been known that renal function is frequently abnormal in patients with hyperuricemia and gout.[34,35] Elevated serum urate leads to MSU crystal deposition, tophi formation, advanced gouty arthritis, and uric acid kidney stones, and is associated with progression of CKD.[34] Several observational studies have demonstrated that patients with gout and nongout conditions on urate-lowering therapy had significantly less progression to chronic renal impairment compared with those not on therapy.[36–38] Two large observational studies in Japan have highlighted the association between hyperuricemia and progression of CKD.[39,40] Although these and other studies have demonstrated that lowering serum urate in patients with CKD prevents progression of renal disease, no large randomized controlled trial has shown that lowering serum urate among those with asymptomatic hyperuricemia prevents development of CKD. However, 2 recent prospective studies in patients with established significant CKD showed no benefit of urate-lowering therapy on slowing progression.[41]

CONSIDERATIONS IN PATIENTS WITH GOUT WITH CARDIOVASCULAR DISEASE

Gout is associated with adverse outcomes from cardiovascular disease (CVD).[42] However, it has also been demonstrated that chronically elevated serum urate of greater than 0.36 mmol/L (6.0 mg/dL) is associated with increased total and cardiovascular mortality among patients with gout.[43] These data raise the question whether reducing gout flares or hyperuricemia with urate-lowering therapy will improve outcome from CVD and emphasize the need to treat aggressively the traditional CVD risk factors in patients with gout.

There is a connection between hyperuricemia and increased cardiovascular risk among patients who are not traditionally considered “high risk” from the perspective of CVD in the general population.[44,45] One large prospective study found that hyperuricemia was an independent risk factor of mortality from total CVD and ischemic stroke in the Taiwanese general population.[45]

AGENT SELECTION AND INITIATION OF URATE-LOWERING THERAPY

Our approach to urate-lowering therapy is outlined in Fig. 1.[46] There are several agents that can be used in urate-lowering therapy. Once an agent is selected, serum urate should be checked on a regular basis and urate-lowering therapy should be increased incrementally until the serum urate is at goal (<6.0 mg/dL for most patients and <5.0 mg/dL for patients when more aggressive urate lowering is desired). More aggressive therapy is indicated when a more rapid dissolution of urate deposits is required. If a patient develops a gout flare, the acute attack should be treated, and urate-lowering therapy should not be discontinued.

Xanthine oxidase inhibitors are recommended as first-line urate-lowering agents, with a general preference for allopurinol over febuxostat based on cost and historical experience if no contraindication to allopurinol exists.[46] Allopurinol can likely be used safely, even in patients with CKD, as long as it is started at a low dose (50–100 mg/d) and increased slowly until target serum urate is reached. There should not be any reluctance to increase allopurinol in patients with CKD; dose escalation is seemingly tolerated as long as it is done slowly.[47] The most feared adverse effect is allopurinol hypersensitivity syndrome (AHS), a rare, but potentially fatal cutaneous reaction.[48] This occurs at a rate of a few per 1000 treated patients, and is more common in patients with CKD. Although postulated that this condition is due to a buildup of renally excreted allopurinol or its active metabolite oxypurinol, this process has never been convincingly demonstrated. Asians (particular patients of Han Chinese descent) have an increased risk of AHS.[48] African Americans also have an increased risk and one prospective study demonstrated that both Asians and African Americans have a 3-fold increased risk of developing AHS compared with whites and Hispanics.[49] For this reason, recent American College of Rheumatology guidelines recommend testing for the HLA-B*5801 allele in Asian and African American patients before starting allopurinol.[8] Additional risk factors for AHS include age greater than 60 years, the presence of CKD, and starting allopurinol at greater than 100 mg/d.[49,50] There are studies reporting that starting low doses of allopurinol ($\leq$100 mg/d) will permit subsequent escalation to reach the target serum urate level while preventing the hypersensitivity reaction. Given the rarity of this serious adverse reaction, small studies cannot assure total safety. However, notably there are no direct studies demonstrating that dose reduction of allopurinol will prevent this reaction and following previously proposed dose reductions of allopurinol in the setting of CKD will not permit therapeutic lowering of the serum urate level in the vast majority of patients.

Febuxostat, a nonpurine inhibitor of xanthine oxidase, can be used for urate-lowering therapy if there are contraindications to allopurinol, including a prior allergic reaction to allopurinol.[46,51] As is the case with allopurinol, the lowest dose should be initiated, with incremental dose increases until the target serum urate is reached. Lowering the serum urate level slowly is less likely to induce flares in gouty arthritis from the rapid dissolution of the deposits. The US Food and Drug Administration issued a black box alert that febuxostat increases the risk of death when compared with allopurinol and should only be used in patients with gout who do not tolerate allopurinol. This recommendation was reached based on limited data, including observational studies and a randomized controlled trial of patients with known significant coronary artery disease, which showed that all-cause mortality and cardiovascular mortality were higher among patients on febuxostat than among patients on allopurinol, although the overall rates of major cardiovascular events were similar

between the 2 groups.[52] There are several critiques of the conduct and analysis of this randomized controlled trial including a large lost to follow-up rate, an imbalance in patients on aspirin between the groups, and the absence of any control group. No good biological explanation is known for this result. Additionally, several other studies completed since this trial have not reproduced the result. Another large study asking the same question is nearing completion. Given the limited therapeutic options for patients with gout who require urate-lowering therapy and the potential for adverse metabolic events owing to untreated hyperuricemia, we believe that selective use of febuxostat is still warranted if contraindications to allopurinol exist. CKD alone does not mandate therapy with febuxostat, even though it is not primarily eliminated via renal excretion.

If a patient fails to achieve target serum urate on xanthine oxidase inhibitors, a uricosuric agent such as probenecid can be added if the patient has reasonable renal function.[35,46,53] Potent uricosurics should generally be avoided in patients with a history of kidney stones. Even if there is no history of renal stones, adequate fluid intake is recommended to prevent nephrolithiasis. Probenecid monotherapy can be used; however, this therapeutic strategy may not be effective if serum urate is markedly elevated or if there is renal insufficiency. Lesinurad has been approved as uricosuric therapy in combination with a xanthine oxidase inhibitor,[53] but is currently not available in the United States. Enzyme (uricase) replacement therapy with pegloticase should be considered in specific situations, as discussed elsewhere in this article.

ANTI-INFLAMMATORY PROPHYLAXIS

As can be seen in **Fig. 1**, anti-inflammatory prophylaxis should be initiated before or simultaneously with urate-lowering therapy whenever possible to decrease the chance of the drop in serum urate level precipitating a "mobilization" flare in gouty arthritis.[46] Anti-inflammatory prophylaxis should generally be continued for at least 6 months after the last flare, and typically for longer periods of time if target serum urate is not achieved or if the patient has persistent palpable tophi.[46] Gout flares occur as urate levels change during the titration of urate-lowering therapy and this can provide an impetus for the patient to discontinue urate-lowering therapy unless this phenomenon is well-explained in advance.

The choice of prophylactic agent—colchicine or low to moderate dose NSAIDs—is determined based on patient comorbidities and cost.[46] In cases where there are contraindications to both NSAIDs and colchicine, low-dose prednisone can be considered, although evidence for this approach is not available and anecdotally this strategy seems to be less effective. Daily colchicine is effective in preventing flares while urate-lowering therapy is titrated.[54,55] In a patient with CKD stage 3 or greater, NSAIDs should be avoided and colchicine should be dose reduced or not used at all owing to concerns of toxicity.[35] As discussed elsewhere in this article, caution must be exercised because drug–drug interactions can occur when colchicine is used in combination with CYP3A4 or P-glycoprotein inhibitors, particularly in the setting of CKD. Reversible but significant painful axonal neurotoxicity and vacuolar myopathy have been well-described.

There are strong data demonstrating that IL-1 inhibition provides effective anti-inflammatory prophylaxis. This prophylactic strategy may particularly helpful in patients who have contraindications to colchicine and NSAIDs, but it is not approved by the US Food and Drug Administration and is expensive.

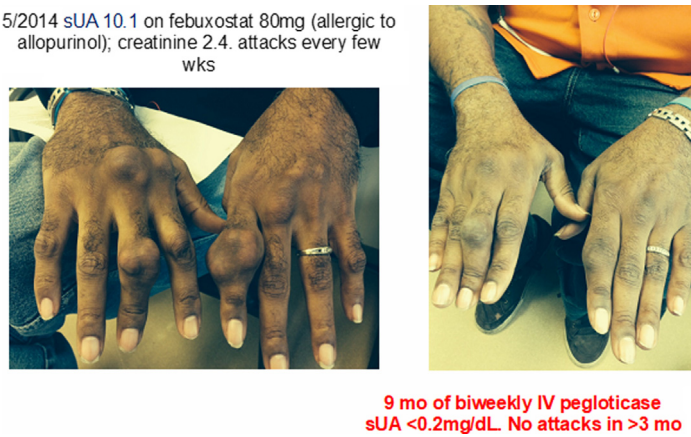

Fig. 2. Efficacy of dramatic lowering of serum urate on tophi.

WHEN TO CONSIDER REFERRAL FOR AGGRESSIVE URATE-LOWERING THERAPY

Pegloticase is a recombinant mammalian uricase conjugated to polyethylene glycol used to dramatically lower the serum urate level and treat refractory gout.[33,56] There are several situations in which patients with gout should be considered for pegloticase administration. If a patient fails to reach the serum urate goal on urate-lowering therapy, then pegloticase should be considered.[46] Pegloticase should be considered if there are contraindications to the administration or optimization of oral urate lowering agents. As outlined in **Fig. 1**, pegloticase should also be considered if urgent resolution of tophi deposition is needed or desired by the patient (eg, nonhealing infected tophus, impending organ transplantation, if the patient is unable to perform daily activities owing to tophus deposition, or if there is a particularly large or burdensome tophus deposition that would likely require years to dissolve with the use of traditional urate-lowering therapy).[46,57,58] Pegloticase is administered every 2 to 3 weeks by intravenous infusion for many months; the duration is based on goals of therapy and the patient's response. Pegloticase can decrease the serum urate level to almost unmeasurable levels, and shrinkage of palpable tophi and improved function of seriously involved joints can be demonstrated over several months (**Fig. 2**). However, in clinical trials approximately 50% of patients rapidly developed high titer drug-neutralizing antibodies to the polyethylene glycol. The drug had only limited (but measurable) benefit in these patients, and those with neutralizing antibodies were more likely to have infusion reactions. Thus, the drug should be discontinued in these patients. Several recent observational studies suggest that coadministration with methotrexate or other immunosuppressive medications may prevent the development of these anti–polyethylene glycol antibodies, and a randomized prospective trial is underway. After a successful course of pegloticase therapy, it is discontinued and traditional urate-lowering therapy is resumed, keeping the serum urate level to approximately 6 mg/dL to prevent recurrence of hyperuricemia and urate deposition. With the dramatic decrease in the serum urate level (often <0.2 mg/dL) with this drug, mobilization flares are expected, and may be severe before the deposits are gone and the flares cease to occur.

CLINICS CARE POINTS

- Gout is the tissue deposition of urate in and around musculoskeletal structures; the major symptom is the painful, usually recurrent flare.
- Gout flares can be eliminated by maintaining a serum urate level well below its saturation point of approximately 6.8 mg/d, which over time will result in the dissolution of the tissue deposits. If urate levels increase again, deposition and flares will recur.
- Gout is diagnosed by the presence of urate crystals in aspirates of swollen joints, bursae or tophae. Demonstration of presumptive urate deposition with characteristic findings on US examination or DECT scan can provide a probable diagnosis. Negative imaging does not exclude the presence of gout.
- Acute gout flares can be treated with colchicine, NSAIDS, glucocorticosteroids or anakinra (an IL-1 antagonist). Therapy must be tailored to the individual patient, taking into account comorbidities and potential medication interactions.
- Start urate-lowering therapy at the lowest dose (ie, allopurinol 50 mg) and slowly increase until serum urate goal is achieved, independent of the renal function. The lower the serum urate level, the more rapid the dissolution of deposits.
- Start low-dose colchicine with urate-lowering therapy to prevent gout flares. The dose should be adjusted for renal function and usually continued if tolerated for 6 months after the last flare and serum urate goal is achieved and palpable tophi resolved.
- Do not stop urate-lowering therapy during gout flares.

DISCLOSURE

S.F. Keller has nothing to disclose. B.F. Mandell: Clinical Investigator: Horizon Pharmaceuticals, Consultant: Horizon Pharmaceuticals, Takeda Pharmaceuticals.

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