

Treatment of Gout

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Gout is the most common inflammatory arthritis with an incidence of approximately 4% in U.S. adults.¹ The annual estimated cost of treating gout in the U.S. is \$1 billion.¹ Pharmacological therapies are key to both symptom management and treatment of the underlying pathophysiology of gout. The purpose of this article is to discuss treatment recommendations provided by updated guidelines from the American College of Physicians (ACP) and the European League Against Rheumatism (EULAR).^{1,2} In addition, the evidence for lesinurad (Zurampic[®]), the new uricosuric agent for chronic gout, will be reviewed.³

Review of Gout

The etiology of gout stems from high serum urate levels that exceed the saturation point in the blood leading to crystals that deposit in cartilage, bones, tendons and other sites. Guidelines recommend that serum urate levels be lowered to less than 6 mg/dL for most patients with gout when hypouricemic therapy is needed.^{2,4,5} Gout attacks usually begins with acute flares and over the years can become chronic in nature. Typical presentation of acute gout is pain in a single joint usually in the lower extremity and is characterized by attacks of pain and inflammation lasting 7-14 days which are self-limiting.¹ Chronic gout develops after multiple acute attacks, and results in chronic persistent inflammation, multiple joint involvement, and the development of tophi and bone damage.¹ Asymptomatic hyperuricemia is very common; however, there is no evidence to support urate-lowering treatment as a preventative strategy for progression to symptomatic gout.⁶

Treatment of Gout

The goal of treating acute gout is to minimize inflammation and the goal of treating chronic gout is to lower serum uric acid and dissolve the crystals that have formed.^{1,7,8} Treatment for acute gout should be started as soon as possible after an attack has started (within 24 hours of onset).⁴ Monotherapy with an oral NSAID, a systemic corticosteroid, or colchicine is recommended for an acute gout flare of mild to moderate severity. Comparative evidence has found similar efficacy for therapies used for acute gout flares. Treatment selection should be based on patient tolerability and comorbidities. Gastrointestinal (GI) adverse events (nausea, vomiting, diarrhea and cramping) have been a limiting factor in the utilization of colchicine. NSAIDs may cause dyspepsia, GI ulcers and bleeding. Corticosteroids are associated with mood disorders, immune suppression and blood glucose elevations.¹ Severe acute gout attacks (consisting of severe pain or polyarticular involvement) can be treated with combination therapy, which could include 1) an NSAID and colchicine; 2) an oral corticosteroid and colchicine; or 3) intra-articular steroid injections and one of the oral treatment options.⁴ Although acute gout tends to resolve in 5-7 days, frequently much more prolonged therapy up to several weeks may be needed.²

Chronic gout is treated with urate lowering therapy (ULT) with the intent of reducing serum uric acid concentrations. Lowering the serum urate level to less than 5-6 mg/dl allows the urate crystals already formed in tissues to dissolve. Patients who have had only one attack, or have very infrequent attacks, may not need ULT. However, ULT should be started in patients who have more than 2 attacks per year, polyarticular attacks, or have begun developing tophi.⁷ Xanthine oxidase inhibitors (XOI), allopurinol or febuxostat, are recommended as first-line options to lower urate levels.^{1,2,7} Secondary options include the uricosurics probenecid or lesinurad. However, probenecid is recommended over lesinurad due to limited evidence for efficacy of lesinurad and concerning renal adverse effects, such as reversible and non-reversible elevations in serum creatinine and acute renal failure.³ If XOI monotherapy fails to lower serum urate levels to target, combination therapy with a XOI and probenecid can be used.⁷ With any of these options, clinical benefit requires that the serum urate level drops to 5-6 mg/dl. There are no "standard" dose for these drugs, and the dose may require

adjustment to achieve this uric acid level. Serum urate levels should be checked every 2-5 weeks during the dose titration phase and every 6 months once a maintenance dose is determined.¹ There is no evidence-based recommendation on duration of ULT therapy; however, common practice is to continue ULT indefinitely to prevent gout attack reoccurrence.

The patient may have more frequent episodes of gout in the 6-12 months after starting ULT. To prevent these flares, prophylactic anti-inflammatory therapy should be started along with ULT. Due to increased risk of flares when initiating ULT, low dose colchicine is recommended first-line for prophylaxis of acute gout flares and a low dose NSAID is recommended as an alternative. Low dose prednisone or prednisolone are also suggested as alternatives to first-line agents in some patients but should be limited due to their long-term adverse effects.⁵ Acute gout prophylaxis is recommended for at least the first 6 months of ULT. Historically, it was recommended that ULT be started 2 weeks after an acute flare subsided, because ULT was thought to increase the risk of acute gout flares upon initiation. However, there is limited evidence that such a delay is necessary.⁷

Guideline Recommendations

American College of Physicians Management of Gout Guidelines

In 2016, the ACP published a new guideline on the management of acute and recurrent gout.¹ Four main recommendations were issued based on moderate to high-quality evidence:

- Evidence supports the use of corticosteroids, NSAIDs or colchicine for treatment of inflammation of acute gout;
- If colchicine is used, then low-dose colchicine as opposed to high dose colchicine, is recommended for acute gout flare treatment;
- Long-term ULT is not recommended for most patients after the first gout attack or for those with infrequent attacks; and
- Patients should be made aware of the benefits, harms and costs, and individual preferences should be discussed before initiating ULT, including concomitant prophylaxis for acute gout flares

EULAR 2016 Guideline on the Management of Gout

Updated EULAR guidelines recommend treatment strategies based upon acute versus chronic treatment.² First-line recommendations for acute gout flares are as follows:

- colchicine (within 12 hours of symptom onset); and/or
- NSAID; or
- Oral corticosteroid; or
- Articular aspiration and injection of corticosteroids

Prophylaxis with colchicine (0.5-1 mg/day in patients with normal renal function) against an acute gout flare is recommended in the first 6 months of ULT.² NSAIDs can also be used as an alternative option. If ULT is indicated, allopurinol 100 mg/day, titrating every 2-4 weeks to a maximum dose of 300 mg/day if needed (in patients with normal renal function) is recommended first line. If serum urate targets are not met after appropriate dose titration of allopurinol, then patients should be switched to febuxostat or a uricosuric (probenecid or lesinurad) with or without allopurinol.² Dose adjustments for patients with renal impairment are required for colchicine, NSAIDs and allopurinol.

Lesinurad

Lesinurad is a new uricosuric agent which increases excretion of uric acid in a mechanism similar to probenecid.³ Lesinurad was approved for use in combination with a XOI when a XOI alone fails to lower serum urate levels to target. Approval for lesinurad was based on three phase 3, double-blind, randomized, placebo-controlled clinical trials lasting 12 months.⁹⁻¹¹ The primary

endpoint was the proportion of subjects who had a serum uric acid level less than 5.0 mg/dL or 6.0 mg/dL. An additional study was initiated to investigate the efficacy and safety of lesinurad monotherapy, but this study was prematurely discontinued by the sponsor for concerns of renal-associated adverse events.¹⁰

Efficacy

All three studies were conducted in adults between 22-82 years of age with hyperuricemia and gout diagnosis on a stable dose of a XOI. Patients had to have at least 2 gout flares in one year or less to be included. Patients with a creatinine clearance of less than 30 mL/minute were excluded and the majority of patients had normal renal function. All patients had the option to receive routine colchicine or NSAID of unknown doses with or without a proton pump inhibitor through month 5 for prevention of gout flares.⁹⁻¹¹ Patients with significant cardiac disease or hepatic disease were excluded. The majority of patients enrolled in these trials were white males.

In one of the trials (n= 603 patients), individuals were randomized to daily allopurinol (≥ 300 mg or 200 mg for moderate renal dysfunction) plus one of the following: placebo, lesinurad 200 mg daily, or lesinurad 400 mg daily.^{9,11} In the lesinurad 200 mg arm, 54% of patients obtained the target serum urate level of less than 6 mg/dL compared to 28% in the placebo arm (relative risk [RR] 0.26; 95% CI 0.17 to 0.36; $p < 0.0001$).^{9,11} In the lesinurad 400 mg arm, 59% of patients obtained a serum urate level less than 6 mg/dL (RR 0.31 vs. placebo; 95% CI 0.22 to 0.41; $p < 0.0001$).^{9,11} However, the addition of lesinurad to allopurinol did not reduce gout flares versus allopurinol alone.

In a second study, 610 patients were randomized into similar arms as in the previous study.^{10,11} Serum urate levels were reduced to less than 6 mg/dL in 55% of patients in the lesinurad 200 mg arm, 67% of patients in the lesinurad 400 mg arm, and 23% of patients in the placebo arm (RR 0.32; 95% CI 0.23 to 0.41; $p < 0.0001$ and RR 0.43; 95% CI 0.34 to 0.52; $p < 0.001$ vs. placebo, respectively).^{10,11} Again, the addition of lesinurad to allopurinol did not reduce gout flares versus allopurinol alone.

In a small 12-month trial (n=324), lesinurad was combined with febuxostat 80 mg daily in patients with tophaceous gout.¹¹ Patients were randomized to lesinurad 200 mg daily plus febuxostat, lesinurad 400 mg daily plus febuxostat or placebo plus febuxostat. At month 6, 57% of patients in the lesinurad 200 mg arm, 76% of patients in the lesinurad 400 mg arm and 47% of patients in the placebo arm achieved a serum urate level of less than 5 mg/dL (all used in combination with febuxostat). The number of patients obtaining goal uric acid levels reached statistical significance in the 400 mg lesinurad group compared to placebo with an absolute risk reduction of 29% and a number needed to treat of 4.

Safety

Adverse events associated with lesinurad were dose-related and most commonly upper respiratory tract infections, hypertension, headache and influenza. Overall, adverse events leading to discontinuation occurred in 9.4%, 6.3%, and 5.4% in the lesinurad 400 mg, lesinurad 200 mg, and placebo groups, respectively.¹¹

More serious adverse events were identified in a safety review.¹² Lesinurad was found to have higher rates of death, major adverse cardiac events (MACE), serious adverse events, and rates of serious and non-serious renal adverse events.¹¹ Exposure-adjusted combined incidence of death for lesinurad arms were higher than placebo (0 for placebo; 5 [$< 1\%$] for lesinurad). The incidence of MACE were comparably low in the lesinurad 200 mg arm and placebo arm, but almost doubled in the lesinurad 400 mg arm with the majority of increased events attributed to nonfatal myocardial infarction.¹¹ Blood pressure, cholesterol, and ECG findings appeared to be unaffected by lesinurad. The increased risk of adverse renal events was highest with lesinurad 400 mg daily but lesinurad 200 mg daily was similar to placebo. Increased serum creatinine was the most common adverse event leading to discontinuation in 1.8%, 0.8%, and 0.8% of the lesinurad 400 mg,

lesinurad 200 mg, and placebo arms, respectively.¹¹ A FDA boxed warning identifies risk of acute renal failure with lesinurad, which is more common when used as monotherapy. Therefore, it is recommended that lesinurad only be used with a XOI.³ The studies were not designed to assess long-term safety data or to specifically identify the risk of MACE with lesinurad.

Conclusion

Appropriate and timely management of gout is paramount due to the highly symptomatic nature of the disease. In the last decade new therapies have expanded the serum urate lowering options but have failed to show superiority to previously available agents. Updated guidelines reinforce previous recommendations of traditional gout therapies. Due to low quality evidence, lesinurad is recommended as an option only after other urate lowering therapies have failed to reduce serum urate levels and control gout flares. Based on a review of the evidence, the Oregon Health Plan (OHP) fee-for-service program supports use of NSAIDs as first-line treatment of acute gout flares and for prophylaxis of gout flare when initiating ULT.¹² Allopurinol is recommended first-line for urate lowering therapy when indicated for chronic gout.

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