A REVIEW: GOUT DISEASE

Omkar Potdar[1], Dr.Hemant Kamble[2], Ashvini Andhale[3], Santosh Waghmare[4]

[1,2,3]Department of Pharmacology, [4]Department of Pharmaceutical Chemistry
Loknete Shri Dadapatil Pharate College of Pharmacy,
Mandavgan Pharata, Tal-Shirur, Dist-Pune

***Abstract*: Gout is the most common crystal arthropathy and the leading cause of inflammatory arthritis. It is associated with functional impairment and, for many, a diminished health-related quality of life. Numerous studies have demonstrated the impact of gout and its associated conditions on patient morbidity and mortality. Unfortunately, gout remains under-diagnosed and under-treated in the general community. Despite major advances in treatment strategies, as many as 90% of patients with gout are poorly controlled or improperly managed and their hyperuricemia and recurrent flares continue. The introduction of novel urate-lowering therapies, new imaging modalities, and a deeper understanding of the pathogenesis of gout raise the possibility of better gout care and improved patient outcomes. Here, we spotlight recent advances in the diagnosis and management of gout and discuss novel therapeutics in gout treatment.**

***Keywords*: Gout, Urate-lowering therapy, Gout treatment**

Introduction: While patients and many clinicians view gout as a series of acute episodes of joint inflammation, such flares are merely a symptom of the disease process of monosodium urate deposition in and around joints, tendons and bourse. Thus, the successful treatment of gout depends on maintaining urate lowering therapy (ULT) to correct hyperuricemia, the proximate cause of urate deposition. Treatment strategies have appropriately focused on the prevention of gout flares, but it is increasingly recognized that hyperuricemia also carries significant metabolic, cardiovascular and renal consequences. In this manuscript, we concentrate on the management of urate deposition and acute gout flares.[1-3]

Symptoms

Intense joint pain. Gout usually affects the big toe, but it can occur in any joint. Other commonly affected joints include the ankles, knees, elbows, wrists and fingers. The pain is likely to be most severe within the first four to 12 hours after it begins.

Lingering discomfort. After the most severe pain subsides, some joint discomfort may last from a few days to a few weeks. Later attacks are likely to last longer and affect more joints

Inflammation and redness. The affected joint or joints become swollen, tender, warm and red.

Limited range of motion. As gout progresses, you may not be able to move your joints normally.[5-9,13]

Causes

Gout occurs when urate crystals accumulate in your joint, causing the inflammation and intense pain of a gout attack. Urate crystals can form when you have high levels of uric acid in your blood. Your body produces uric acid when it breaks down purines — substances that are found naturally in your body.

Purines are also found in certain foods, including red meat and organ meats, such as liver. Purine-rich seafood includes anchovies, sardines, mussels, scallops, trout and tuna. Alcoholic beverages, especially beer, and drinks sweetened with fruit sugar (fructose) promote higher levels of uric acid.

Normally, uric acid dissolves in your blood and passes through your kidneys into your urine. But sometimes either your body produces too much uric acid or your kidneys excrete too little uric acid. When this happens, uric acid can build up, forming sharp, needlelike urate crystals in a joint or surrounding tissue that cause pain, inflammation and swelling.[5-13]

Complications

Recurrent gout. Some people may never experience gout signs and symptoms again. Others may experience gout several times each year. Medications may help prevent gout attacks in people with recurrent gout. If left untreated, gout can cause erosion and destruction of a joint.

Advanced gout. Untreated gout may cause deposits of urate crystals to form under the skin in nodules called tophi (TOE-fie). Tophi can develop in several areas, such as your fingers, hands, feet, elbows or Achilles tendons along the backs of your ankles. Tophi usually aren't painful, but they can become swollen and tender during gout attacks.

Kidney stones. Urate crystals may collect in the urinary tracts of people with gout, causing kidney stones. Medications can help reduce the risk of kidney stones.

Diagnosis

Doctors usually diagnose gout based on your symptoms and the appearance of the affected joint. Tests to help diagnose gout may include:

Joint fluid test your doctor may use a needle to draw fluid from your affected joint. Urate crystals may be visible when the fluid is examined under a microscope.

Blood test your doctor may recommend a blood test to measure the levels of uric acid in your blood. Blood test results can be misleading, though. Some people have high uric acid levels, but never experience gout. And some people have signs and symptoms of gout, but don't have unusual levels of uric acid in their blood.

X-ray imaging Joint X-rays can be helpful to rule out other causes of joint inflammation.
Ultrasound This test uses sound waves to detect urate crystals in joints or in tophi.
Dual-energy computerized tomography This test combines X-ray images taken from many different angles to visualize urate crystals in joints.[6-16,20]

Treatment

Gout medications are available in two types and focus on two different problems. The first type helps reduce the inflammation and pain associated with gout attacks. The second type works to prevent gout complications by lowering the amount of uric acid in your blood.
Which type of medication is right for you depends on the frequency and severity of your symptoms, along with any other health problems you may have.

Nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs include over-the-counter options such as ibuprofen (Advil, Motrin IB, others) and naproxen sodium (Aleve), as well as more-powerful prescription NSAIDs such as indomethacin. NSAIDs carry risks of stomach pain, bleeding and ulcers.
Colchicine. Your doctor may recommend colchicine, an anti-inflammatory drug that effectively reduces gout pain. The drug's effectiveness may be offset, however, by side effects such as nausea, vomiting and diarrhea.
Corticosteroids. Corticosteroid medications, such as prednisone, may control gout inflammation and pain. Corticosteroids may be in pill form, or they can be injected into your joint. Side effects of corticosteroids may include mood changes, increased blood sugar levels and elevated blood pressure.[15-21]

New approaches to serum urate lowering

Hyperuricemia is the underlying condition promoting gout, long-term treatment of gout almost always involves the therapeutic lowering of serum and tissue sUA levels.
Pegloticase : Pegloticase is a recombinant, pegylated uricase that degrades uric acid. Pegloticase is administered intravenously every 2 weeks. Studies confirm the ability of pegloticase to rapidly and dramatically lower sUA and to promote the often-dramatic resolution of tophi. Several safety considerations arose during randomized controlled trials of pegloticase.
Lesinurad : Lesinurad is a selective, highly potent uric acid reabsorption inhibitor. In contrast to the older uricosuric probenecid, lesinurad is more potent and remains effective even in moderate renal insufficiency. lesinurad is approved only at the 200 mg dose and only in conjunction with an XOI. Baseline assessment and periodic testing of renal function are required, particularly for patients with creatinine clearance below 60 mL/min.
Arhalofenate: Arhalofenate is a pipeline drug with a dual mechanism of action. Patients initiating ULT are routinely prescribed concurrent anti-inflammatory prophylaxis to reduce the risk of gout attacks precipitated by the sUA-lowering process itself. Historically, all gout medications have been either anti-inflammatory or sUA-lowering. In contrast, arhalofenate, a peroxisome proliferator-activated receptor-gamma (PPAR-γ) partial agonist, demonstrates dual ULT and anti-inflammatory effects.[15-21,9,8]

References

1. Singh J.A. Challenges faced by patients in gout treatment: a qualitative study. *J Clin Rhellllllumatol: Practical Rep Rheum Musculoskelet Dis.* 2014;20(3):172–174.
2. Kanbara A., Seyama I. Effect of urine pH on uric acid excretion by manipulating food materials. *Nucleosides, Nucleotides Nucleic Acids.* 2011;30(12):1066–1071.
3. Enomoto A., Endou H. Roles of organic anion transporters (OATs) and a urate transporter (URAT1) in the pathophysiology of human disease. *Clin Exp Nephrol.* 2005;9(3):195–205.
4. Tan P.K., Ostertag T.M., Miner J.N. Mechanism of high affinity inhibition of the human urate transporter URAT1. *Sci Rep.* 2016;6:34995.
5. Phipps-Green A.J., Merriman M.E., Topless R., Altaf S., Montgomery G.W., Franklin C. Twenty-eight loci that influence serum urate levels: analysis of association with gout. *Ann Rheum Dis.* 2016;75(1):124–130.
6. Kolz M., Johnson T., Sanna S., Teumer A., Vitart V., Perola M. Meta-analysis of 28,141 individuals identifies common variants within five new loci that influence uric acid concentrations. *PLoS Genet.* 2009;5(6):e1000504.
7. Cronstein B.N., Sunkureddi P. Mechanistic aspects of inflammation and clinical management of inflammation in acute gouty arthritis. *J Clin Rheumatol: Practical Rep Rheumat Musculoskelet Dis.* 2013;19(1):19.
8. Busso N., Ea H.K. The mechanisms of inflammation in gout and pseudogout (CPP-induced arthritis) *Reumatismo.* 2012;63(4):230–237.
9. Ea H.K. Mechanisms of gout inflammation. *Presse Med.* 2011;40(9 Pt 1):836–843.
Dalbeth N., Lauterio T.J., Wolfe H.R. Mechanism of action of colchicine in the treatment of gout. *Clin Ther.* 2014;36(10):1465–1479.
10.Steiger S., Harper J.L. Mechanisms of spontaneous resolution of acute gouty inflammation. *Curr Rheumatol Rep.* 2014;16(1):392.
11. Grassi W., De Angelis R. Clinical features of gout. *Reumatismo.* 2012;63(4):238–245.
12. Gonzalez E.B. An update on the pathology and clinical management of gouty arthritis. *Clin Rheumatol.* 2012;31(1):13–21.
13. Schlesinger N., Thiele R.G. The pathogenesis of bone erosions in gouty arthritis. *Ann Rheum Dis.* 2010;69(11):1907–1912.

14. Kosmadakis G., Viskaduraki M., Michail S. The validity of fractional excretion of uric acid in the diagnosis of acute kidney injury due to decreased kidney perfusion. *Am J Kidney Dis.* 2009;54(6):1186–1187.
15. Burns C.M., Wortmann R.L. Latest evidence on gout management: what the clinician needs to know. *Therap Adv Chronic Dis.* 2012;3(6):271–286.
16. Kanbay M., Huddam B., Azak A., Solak Y., Kadioglu G.K., Kirbas I. A randomized study of allopurinol on endothelial function and estimated glomular filtration rate in asymptomatic hyperuricemic subjects with normal renal function. *Clin J Am Soc Nephrol: CJASN.* 2011;6(8):1887–1894.
17. Luk A.J., Levin G.P., Moore E.E., Zhou X.H., Kestenbaum B.R., Choi H.K. Allopurinol and mortality in hyperuricaemic patients. *Rheumatol (Oxford, England)* 2009;48(7):804–806.
18. 38. Yokose C., Chen M., Berhanu A., Pillinger M.H., Krasnokutsky S. Gout and osteoarthritis: associations, pathophysiology, and therapeutic implications. *Curr Rheumatol Rep.* 2016;18(10):65
19. Mazzali M., Kanbay M., Segal M.S., Shafiu M., Jalal D., Feig D.I. Uric acid and hypertension: cause or effect? *Curr Rheumatol Rep.* 2010;12(2):108–117.
20. Katsiki N., Papanas N., Fonseca V.A., Maltezos E., Mikhailidis D.P. Uric acid and diabetes: Is there a link? *Curr Pharm Des.* 2013;19(27):4930–4937.
21. Roddy E. Revisiting the pathogenesis of podagra: why does gout target the foot? *J Foot Ankle Res.* 2011;4(1):13.
22. Canoso J.J., Yood R.A. Acute gouty bursitis: report of 15 cases. *Ann Rheum Dis.* 1979;38(4):326–328.