WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 4, 571-581. Review Article ISSN 2277– 7105

A REVIEW: GOUT AND ITS MANAGEMENT

Anu Sebastian[1], Anusha Shaji[2]* and Akshay Murali[3]

[1,2]Assistant Professor, Department of Pharmacology, Nirmala College of Pharmacy, Ernakulam.

[3]Assistant Professor, Department of Pharmaceutical Chemistry, St. Joseph College of Pharmacy, Cherthala.

Article Received on
06 Feb. 2020,
Revised on 27 Feb. 2020,
Accepted on 18 March 2020
DOI: 10.20959/wjpr20204-17138

***Corresponding Author**
Anusha Shaji
Assistant Professor, Department of Pharmacology, Nirmala College of Pharmacy, Ernakulam.

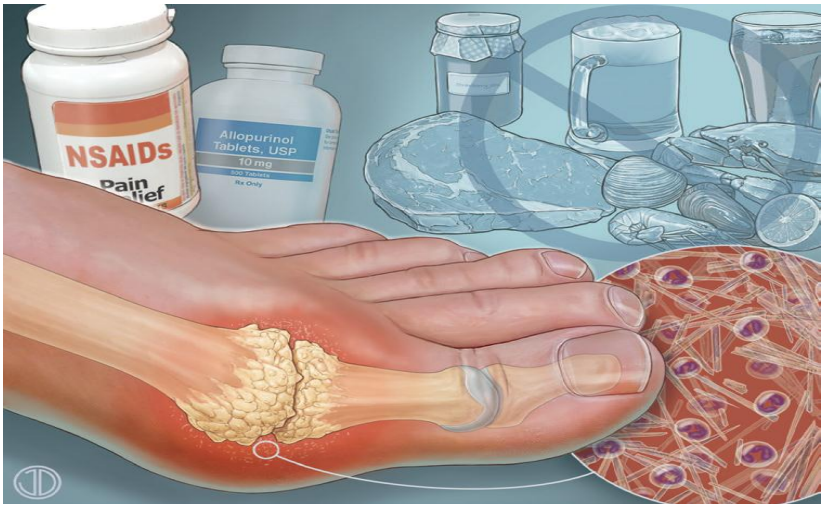
ABSTRACT

Gout is a disease in which defective metabolism of uric acid causes arthritis, especially in the smaller bones of the feet, deposition of chalk- stones, and episodes of acute pain. The majority of gout cases are treated with medication. Medication can be used to treat the symptoms of gout attacks, prevent future flares, and reduce the risk of gout complications such as kidney stones and the development of trophy. Commonly used medications include nonsteroidal anti inflammatory drugs (NSAIDs), colchicine or corticosteroids.

KEYWORDS: Gout, Acute gout, Chronic gout, NSAIDs.

INTRODUCTION

Gout is the most common cause of inflammatory arthritis worldwide. It is characterised by deposition of monosodium urate crystals in joints and tissues and usually presents with intermittent painful attacks followed by long periods of remission.[1] Pain typically comes on rapidly, reaching maximal intensity in less than 12 hours. The joint at the base of the big toe is affected in about half of cases. It may also result in tophi, kidney stones, or urate nephropathy.[2] Although the prevalence of gout is equal in men and women, men are six times more likely to have serum uric acid concentrations above 7 mg per dL (420 μmol per L). Gout typically occurs during middle age and is uncommon before the age of 30 years. Women rarely have gouty arthritis attacks before menopause.[3]



SIGNS AND SYMPTOMS

Gout can present in multiple ways, although the most usual is a recurrent attack of acute inflammatory arthritis (a red, tender, hot, swollen joint).[4] The metatarsal-phalangeal joint at the base of the big toe is affected most often, accounting for half of cases. Other joints, such as the heels, knees, wrists, and fingers, may also be affected. Joint pain usually begins over 2–4 hours and during the night.[5] This is mainly due to lower body temperature.[6] Other symptoms may rarely occur along with the joint pain, including fatigue and a high fever.[5,6]

Long-standing elevated uric acid levels (hyperuricemia) may result in other symptoms, including hard, painless deposits of uric acid crystals known as tophi. Extensive tophi may lead to chronic arthritis due to bone erosion.[7] Elevated levels of uric acid may also lead to crystals precipitating in the kidneys, resulting in stone formation and subsequent urate nephropathy.

ETIOLOGY

The crystallization of uric acid, often related to relatively high levels in the blood, is the underlying cause of gout. This can occur because of:

- Diet
- Genetic Predisposition, or
- Underexcretion of urate, the Salts of uric acid.[4]

Underexcretion of uric acid by the kidney is the primary cause of hyperuricemia in about 90% of cases, while overproduction is the cause in less than 10%.[2] About 10% of people

with hyperuricemia develop gout at some point in their lifetimes.[8] The risk, however, varies depending on the degree of hyperuricemia. When levels are between 415 and 530 μmol/l (7 and 8.9 mg/dl), the risk is 0.5% per year, while in those with a level greater than 535 μmol/l (9 mg/dL), the risk is 4.5% per year.[6]

Diet

Ingestion of foods rich in purines such as cooked or processed food especially from animal and seafood origin is a key element of increasing uric acid precursors. While foods rich in purine of vegetable origin such as beans, lentils, mushrooms, peas, legumes, and dairy products do not carry any risk on hyperuriceamia and gout, thus, can be allowed in gout patients. Vitamin C was found to increase renal excretion of uric acid so it can be used as a supplement during management of gout. Alcohol is a well-known risk factor for gout. For instance, beer is the worst in increasing the risk for gout compared to liquor. While the lowest risk among alcoholic drinks was for wine.[9]

Genetic Predisposition

SLC22A12 gene encodes for the transporter URAT1 present on the apical membrane of renal tubules. SLC2A9 is another gene involved in regulation of UA excretion. It encodes for a transporter protein in the membrane of renal tubules. Polymorphism of both genes results in decreased fractional excretion of UA leading to increased SUA levels. ABCG2 is a gene transporter for UA in the proximal tubular cells of the kidney as well as in the GIT. *SLC17A1, SLC17A3* genes are important determinants of SUA levels acting as membrane transporters in the kidenys. Other genes involved in determination of SUA levels include SLC22A11, the glucokinase regulatory protein (GCKR), Carmil (LRRC16A), and near PDZ domain containing 1 (PDZK1) genes.[10,11]

Underexcretion Of Urate

Two thirds of urate excretion occurs in the kidneys while the rest is excreted through the gastrointestinal tract (GIT). Reduced secretory function of the transporter ABCG2 leads to decreased excretion of uric acid through the GIT resulting in rise of serum levels of uric acid and enhanced renal excretion.[12,13]

Uric acid crystals are not soluble so require specific membrane transporters in order to cross cell membranes. Of these transporters are the urate transporter/channel (URAT) mainly URAT1 and the organic anion transporters (OAT1 and OAT3).[12,14]

Renal excretion of uric acid is the end result of 4 phases. The first phase is the passage of UA across the Bowman's capsule (glomerular filtration); followed by reabsorption of almost all urates passing in the proximal tubules. The third phase involves secretion of part of the reabsorbed UA ending with another reabsorption phase in the proximal tubules. The excreted UA is almost 10% of the filtered urate through Bowman's capsule and the rest is reabsorbed in the body.[15]

Reduced renal excretion of urate is associated with some autosomal dominant disorders. Uromodulin is a gene that is expressed in the thick ascending limb of the loop of henle. It is responsible for regulating water permeability. Mutations of uromodulin gene result in decreased fractional excretion of UA, which in turn increases SUA.[16]

PATHOPHYSIOLOGY

Gout is a disorder of purine metabolism,[2] and occurs when its final metabolite, uric acid, crystallizes in the form of monosodium urate, precipitating and forming deposits (tophi) in joints, on tendons, and in the surrounding tissues.[7] Microscopic tophi may be walled off by a ring of proteins, which blocks interaction of the crystals with cells and therefore avoids inflammation. Naked crystals may break out of walled-off tophi due to minor physical damage to the joint, medical or surgical stress, or rapid changes in uric acid levels.[17] When they break through the tophi, they trigger a local immune-mediated inflammatory reaction in macrophages, which is initiated by the NLRP3 inflammasome protein complex.[7,17,18] Activation of the NLRP3 inflammasome recruits the enzyme caspase 1, which converts pro-interleukin 1β into active interleukin 1β, one of the key proteins in the inflammatory cascade.[18]

The triggers for precipitation of uric acid are not well understood. While it may crystallize at normal levels, it is more likely to do so as levels increase.[7,19] Other triggers believed to be important in acute episodes of arthritis include cool temperatures, rapid changes in uric acid levels, acidosis[20,21], articular hydration and extracellular matrix proteins, such as proteoglycans, collagens, and chondroitin sulfate.[2] The increased precipitation at low temperatures partly explains why the joints in the feet are most commonly affected.[4]

DIAGNOSIS

The best way to diagnose gout is for a doctor to examine the fluid lining the affected joint (synovial fluid) under a microscope to look for urate crystals. To do this, he or she uses a

needle and syringe to withdraw a small amount of fluid from inside the joint. Tophi located just beneath the skin can also be sampled with a needle to diagnose tophaceous gout.

If it is not possible to do a synovial fluid analysis, a doctor can make a tentative diagnosis of gout based on your symptoms, a physical examination, and blood tests.[22]

Blood tests

Hyperuricemia is defined as a plasma urate level greater than 420 μmol/l (7.0 mg/dl) in males and 360 μmol/l (6.0 mg/dl) in females.[23] Other blood tests commonly performed are white blood cell count, electrolytes, kidney function and erythrocyte sedimentation rate (ESR). However, both the white blood cells and ESR may be elevated due to gout in the absence of infection.[24,25] A white blood cell count as high as 40.0×10^9/l (40,000/mm^3) has been documented.[6]

MANAGEMENT

To achieve rapid and complete resolution of symptoms, treatment of acute gout should commence within 24 hours of symptom onset. Oral corticosteroids, intravenous corticosteroids, NSAIDs, and colchicine are equally effective in treating acute flares of gout. NSAIDs are the first-line treatment. Indomethacin (Indocin) has historically been the preferred choice; however, there is no evidence it is more effective than any other NSAID. Intramuscular ketorolac appears to have similar effectiveness. Any oral NSAID may be given at the maximal dosage and continued for one to two days after relief of symptoms.

Corticosteroids are an appropriate alternative for patients who cannot tolerate NSAIDs or colchicines. Patients with diabetes mellitus can be given corticosteroids for short-term use with appropriate monitoring for hyperglycemia. When gout is limited to a single joint, intra-articular corticosteroid injections may be preferable to systemic corticosteroids because of their lower adverse effect profile. Rebound flares are common after discontinuation of corticosteroid therapy for acute gout. To reduce the risk of a rebound flare, preventive treatment and initiation of a tapered course of corticosteroids over 10 to 14 days is recommended after resolution of symptoms.

Colchicine is another treatment option for acute gout. Generic colchicine, which has been used for decades, did not undergo formal review by the U.S. Food and Drug Administration (FDA) for this indication until 2009, when branded colchicine (Colcrys) was approved.

However, Colcrys is expensive, and generic colchicine is no longer available. In addition, colchicine does not have analgesic properties and may be less effective in treating acute flares when given beyond 72 to 96 hours after symptom onset. Common adverse effects include nausea, vomiting, and diarrhea. Colchicine should be used with caution in patients with hepatic or renal impairment.

Prevention

Serum urate–lowering therapy should be initiated to prevent recurrences in persons with a history of gout and any one of the following: at least two flares per year (one per year in persons with chronic kidney disease stage 2 or greater), tophi, or a history of nephrolithiasis.

Serum urate should be lowered to a target of less than 5 to 6 mg per dL (297 to 357 μmol per L), depending on the crystal and tophaceous burden. Normal serum urate levels do not exclude the diagnosis of gout. They should be monitored periodically to assess preventive therapy in patients with recurrent gout and a history of elevated urate levels.[12] Urate-lowering therapy should be continued for three to six months after a flare if there are no ongoing symptoms. Therapy should continue indefinitely if there are ongoing signs or symptoms (e.g., one or more tophi on examination).[18]

Dietary Modifications

Weight gain is a significant risk factor for gout in men, whereas weight loss reduces the risk.[2] Intake of high-fructose corn syrup should be restricted[18], because the fructose contributes to increased uric acid production as a byproduct of adenosine triphosphate catabolism. Patients with gout should limit their intake of purine-rich animal protein (e.g., organ meats, beef, lamb, pork, shellfish) and avoid alcohol (especially beer). Purine-rich vegetables do not increase the risk of gout.[8,9] Consumption of vegetables and low-fat or nonfat dairy products should be encouraged.

Pharmacologic Options

Pharmacologic options for prevention of acute and chronic gout are outlined in Table 1 and Table 2. Although avoidance of loop and thiazide diuretics has been recommended for patients with hypertension and gout because these agents can increase uric acid levels, a systematic review found only small increases in the risk of gouty flares. Calcium channel blockers and the angiotensin receptor blocker losartan (Cozaar) are associated with a

decreased risk of incident gout. Losartan is the only angiotensin receptor blocker with this property.

Historically, urate-lowering medication was thought to worsen acute gout flares, but recent evidence suggests that allopurinol (Zyloprim) can be started during an acute flare if it is used in conjunction with an NSAID and colchicine. Patients receiving a urate-lowering medication should be treated concurrently with an NSAID, colchicine, or low-dose corticosteroid to prevent a flare. Treatment should continue for at least three months after uric acid levels fall below the target goal in those without tophi, or for six months in those with a history of tophi. NSAIDs and corticosteroids should not be used for long periods without a urate-lowering medication because uric acid crystals continue to accumulate and damage the joint, despite a lack of pain or clinical signs of inflammation. If a patient has gout flare while receiving a urate-lowering agent, the medication should be continued while the flare is treated acutely.

Table 1: Medications for Treatment of Acute Gout.

Medication	***Example regimen***	***Notes***
NSAIDs	Indomethacin (Indocin), 50 mg three times per day	First-line therapy; all NSAIDs are equally effective; adverse effects include gastric bleeding and kidney injury
Colchicine (Colcrys)	1.2 mg initially, then 0.6 mg one hour later, then 0.6 to 1.2 mg per day	No analgesic properties; gastrointestinal adverse effects are common; avoid use in patients with renal and hepatic insufficiency; contraindicated in patients receiving clarithromycin (Biaxin)
Corticosteroids	Oral, intramuscular, or intra-articular routes, variable dosing (e.g., prednisone, 40 mg for four days, then 20 mg for four days, then 10 mg for four days)	Preferred therapy for patients in whom NSAIDs and colchicine are contraindicated; when discontinuing oral corticosteroids, taper to avoid rebound flares

Table 2: Medications for Prevention of Chronic Gout.

Medication	***Dosage***	***Notes***
Colchicine (Colcrys)	0.6 to 1.2 mg per day	May cause reversible axonal neuromyopathy; may increase risk of rhabdomyolysis when used with statins or clarithromycin (Biaxin)
Pegloticase (Krystexxa)	8 mg intravenously every two weeks	Indicated for refractory gout; expensive (more than $5,000 per dose28)
Probenecid	250 mg two times per day initially; titrate up to 2 g per day	High risk of nephrolithiasis; encourage hydration and urine alkalization with potassium citrate; multiple drug interactions
Xanthine oxidase inhibitors:		
Allopurinol	100 mg per day initially, except in	Genetic testing recommended before

(Zyloprim)	patients with renal dysfunction; common effective dosage is 300 mg per day, but higher dosages may be needed	initiating treatment in patients at risk of severe hypersensitivity skin reaction (those of Han Chinese or Thai descent, regardless of kidney function, or Koreans with chronic kidney disease stage 3 or greater)
Febuxostat (Uloric)	40 mg once per day; may increase up to 80 mg per day if serum uric acid level > 6 mg per dL (357 μmol per L) after two weeks	Contraindicated in patients receiving azathioprine (Imuran) and mercaptopurine

Allopurinol

Allopurinol, a xanthine oxidase inhibitor, is a first-line agent to prevent recurrent gout. In patients with gout and chronic kidney disease or congestive heart failure, allopurinol has the added benefit of preventing chronic disease progression. The starting dosage is 100 mg per day, and 300 mg per day is a common maintenance dosage. Dosing is guided by the target serum uric acid level.[9,20] In patients with chronic kidney disease, low initial doses are recommended with slow titration to achieve target uric acid levels. Dosages higher than 300 mg may be used—even in those with renal impairment—as long as patients are closely monitored for adverse effects.[7] Certain ethnic groups have a higher risk of a severe hypersensitivity skin reaction when starting allopurinol therapy. Screening for human leukocyte antigen-B*5801 genotype is recommended before initiating treatment in patients of Han Chinese or Thai descent, regardless of kidney function, or in Koreans with chronic kidney disease stage 3 or greater.[14]

Probenecid

Probenecid increases urinary excretion of uric acid and is typically used as a second-line treatment because of numerous drug interactions. Of particular concern, probenecid increases blood levels of methotrexate and ketorolac, which may result in severe toxicity. Probenecid may be used in combination with allopurinol or febuxostat when one drug does not independently lower serum uric acid to target levels. Nephrolithiasis is a common adverse effect that may be avoided by high fluid intake and urine alkalization with potassium citrate.[14]

Colchicine

Colchicine prevents gout flares at a dosage of 0.6 to 1.2 mg per day. The dose should be adjusted in patients with chronic kidney disease and when used with cytochrome P450 3A4 or P-glycoprotein inhibitors. The long-term adverse effects of colchicine include reversible

axonal neuromyopathy (less than 1%). Patients should be advised to stop taking colchicine and tell their physician if they experience leg weakness or pain. Treatment should be discontinued if any signs or symptoms of nerve or muscle damage are present. The rare risk of rhabdomyolysis is increased when colchicine is used concomitantly with statins or clarithromycin (Biaxin), especially in older adults or those with chronic kidney disease; therefore, close monitoring is recommended.[17]

Febuxostat

Febuxostat (Uloric) is a xanthine oxidase inhibitor that was approved by the FDA in 2009. Although febuxostat is superior to 300 mg allopurinol at lowering serum uric acid levels, it is not more effective at reducing the frequency of gout flares.[12] Febuxostat is considered a first-line agent to prevent recurrent gout[9], but it is considerably more expensive than allopurinol.

Pegloticase

Pegloticase (Krystexxa) is an intravenous uricase approved by the FDA in 2010. The mechanism of action involves metabolism of uric acid to allantoin. It is a third-line agent and is indicated for treatment of refractory gout. It is usually administered by a rheumatologist and is given every two weeks at a cost of more than $5,000 per dose.[18]

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