Chapter

Pharmacology of the Therapeutic Approaches of Gout

Rajit Sahai, Pramod Kumar Sharma, Arup Misra and Siddhartha Dutta

Abstract

Gout is a metabolic disorder characterized by hyperuricemia. Asymptomatic hyperuricemia ought not to be treated until arthritis; renal calculi or tophi become evident. The cornerstone of therapy of acute attack is often nonsteroidal anti-inflammatory drugs (NSAIDs), barring specific situations wherein colchicine and corticosteroids do have a role. Usually NSAIDs with stronger anti-inflammatory action are used in high and quickly repeated doses and have a slower response response as compared to colchicine, they are better tolerated. Colchicine has a unique mechanism action. Intra-articular corticosteroids provide relief in acute attack and are given in patients having inability to tolerate NSAIDs and colchicine. Chronic gout requires treatments with drugs that either promote excretion (e.g., probenecid, lesinurad) or prevent its synthesis through inhibition of enzyme *xanthine oxidase* (allopurinol, febuxostat, etc.). Pegloticase and rasburicase, being a recombinant uricase enzyme, oxidize uric acid to highly soluble allantoin excreted in urine. In spite of these effective treatment modalities, question arises on their safety profile. Newer treatment options are being extensively studied especially interleukin-1 (IL-1) inhibitors but their approval is still pending. The quest for an optimally designed drug with desirable efficacy and acceptable safety profile is still on.

Keywords: gout, hyperuricemia, arthritis, uricosurics, uricase

1. Introduction

Gout is a metabolic disorder characterized by increased deposition of urate crystals in the joints and connective tissue (tophi) and results in episodic acute or chronic arthritis. It also leads to deposition of urate crystals within the renal interstitium or nephrolithiasis [1]. Prevalence of gout has an uneven distribution throughout the globe with a higher prevalence in the Pacific countries. Blacks have been shown to have a decreased incidence/prevalence [2]. Gout affects 3% people of the western population with majority cases seen in middle-aged and elderly men and postmenopausal women [3]. Gout can be either a primary gout which is hereditary or due to genetic anomaly in the genes responsible for excretion of uric acid. Secondary gout is majorly due to acquired causes of hyperuricemia. Deposition of urate crystal occurs when uric acid levels are >6.8 mg/dl.

2. Causes

Gout can result from either increased production or due to decreased excretion of uric acid from the kidney or both. The causes of hyperuricemia can be listed separately into those for primary and secondary hyperuricemia.

1. Primary hyperuricemia
    a. Increased production of purine
        i. Idiopathic
        ii. Enzyme defects (e.g., Lesch-Nyhan syndrome, glycogen storage diseases)
    b. Decreased renal clearance
        i. Idiopathic
2. Secondary hyperuricemia
    a. Increased catabolism and turnover of purine
        i. Myeloproliferative disorders
        ii. Lymphoproliferative disorders
        iii. Carcinoma and sarcoma
        iv. Chronic hemolytic anemia
        v. Cytotoxic drugs
        vi. Psoriasis
    b. Decreased renal clearance
        i. Intrinsic kidney disease
        ii. Drug induced (thiazides, low dose aspirin, pyrazinamide, loop diuretics, ethambutol, levodopa, ethanol cyclosporine, etc.)
        iii. Hyperlactacidemia (lactic acidosis, alcoholism)
        iv. Hyperketoacidemia (diabetic ketoacidosis, starvation)
        v. Diabetes insipidus
        vi. Bartter syndrome [4]

3. Pathophysiology

Following hyperuricemia, the urate crystals get deposited in the joints and connective tissues and activate monocytes or macrophages via Toll-like receptor

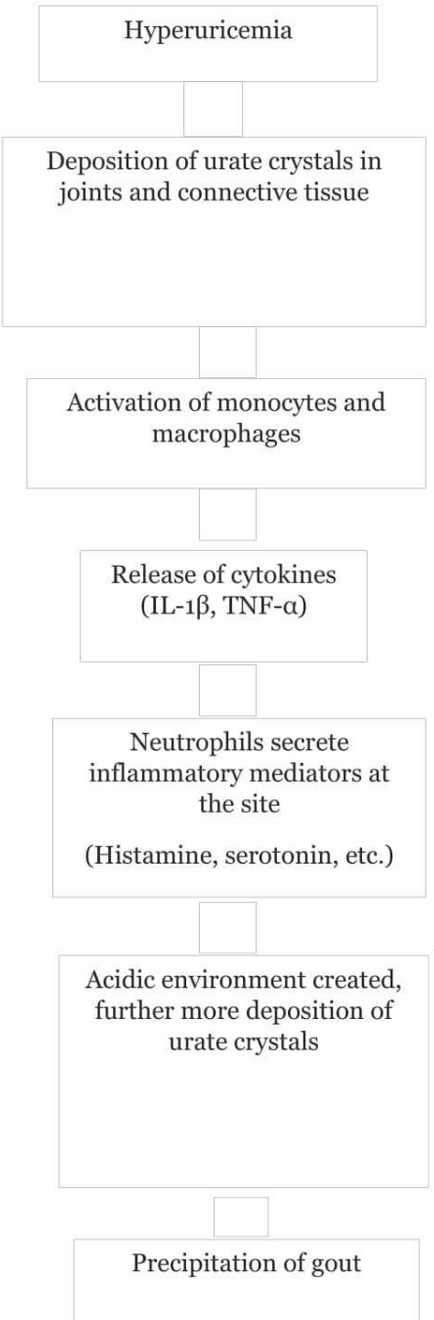

Figure 1.
Schematic illustration of pathophysiology of gout.

pathway mounting and innate immune response. This results in secretion of cytokines including interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) leading to endothelial activation and attraction of neutrophils to the site of inflammation. Neutrophils secrete inflammatory mediators that create an acidic environment, which further causes precipitation of urate crystals (**Figure 1**) [3].

4. Clinical presentation

Acute arthritis is the commonest early presentation of gout. It usually affects one joint precisely the metatarsophalangeal joint of the great toe. However, the disease can also have a polyarticular presentation and involve other joints like tarsal, ankle, or

knee joints. In certain cases, it may also have a periarticular involvement involving the soft tissues. The intensity of the pain increases with the duration of the attack. Joints become swollen, tender with the overlying skin being warm, tense, and red in color. These symptoms most likely are associated with hyperthermia, and with time tophi start developing in the external ears, feet, olecranon, and prepatellar bursa [4, 5].

1. Laboratory investigations:

    a. Serum uric acid levels: Used for diagnosing a patient of gout; however, these could be false positives and false negatives as it may not be raised at the time of the attack. It is also used as a reference while the patient is receiving hypouricemic therapy.

    b. Peripheral leukocyte count is usually elevated during attack.

    c. Aspiration of joint fluid and demonstration of sodium urate crystals are diagnostic. When observed under the microscope, these are needle-shaped crystals present both extracellularly and intracellularly. Increase in the number of crystals within the joint can lead to formation of a thick pasty, chalky joint fluid. When observed under compensated polarized light, the crystals appear to be brightly birefringent with negative elongations. In addition, the leukocyte count of the aspirated fluid is also found to be raised [1, 6].

2. Radiographic imaging:

    a. X-ray: No changes seen in early stage of disease, later punched out erosions with an overhanging rim of cortical bone develop. Presence of this erosion adjacent to tophi is diagnostic.

    b. Ultrasonography: Used when tophi are small and cannot be appreciated physically [4, 5].

5. Management of gout

Treatment modality in gout is aimed at:

1. Reducing the symptoms during acute attack

2. Reducing the recurrent attacks

3. Lowering serum urate levels [3]

Treatment can be divided into non-pharmacological and pharmacological.

5.1 Non-pharmacological treatment

Patients upon being diagnosed with hyperuricemia should be advised diet with less purine content (refined cereals, white bread, milk, peanut butter, fruits, nuts, tomato, green vegetables, etc.). Alcohol consumption should be kept at minimum; intake of whiskey and wine should be preferred rather than beer. Organ meats and beverages sweetened with high fructose corn syrup should be avoided. In addition, high intake of liquid diet should be advised to facilitate urine output of 2 L or more,

which favors urate excretion. Patients with asymptomatic hyperuricemia ought not to be given pharmacological treatment until arthritis or renal calculi develop.

5.2 Pharmacological treatment

Pharmacotherapy of gout is divided into:

1. For acute gout
    a. Nonsteroidal anti-inflammatory drugs (NSAIDs)
    b. Colchicine
    c. Corticosteroids
2. For chronic gout
    a. Uricosurics (probenecid, sulfinpyrazone, benzbromarone, lesinurad)
    b. Uric acid synthesis inhibitors (allopurinol, febuxostat)
    c. Uricase (rasburicase, pegloticase) [7]

5.2.1 For acute gout

1. **NSAIDs:** Oral agents are preferred and are effective of acute gout. The drugs with a stronger anti-inflammatory action are used. They provide relief by inhibiting cyclooxygenase-2(COX-2)-mediated prostaglandin synthesis at the site of injury; however, there are certain additional mechanisms pertaining to some drugs also. The NSAIDs provide symptomatic relief from pain and inflammation. In addition, they are also used initially as a bridging therapy along with uric acid synthesis inhibitors to prevent development of symptoms of acute gouty arthritis due to mobilization of urate from the tissues. NSAIDs are contraindicated in conditions like active peptic ulcer disease, impaired kidney function, and history of allergic reactions. The drugs used more often are naproxen, piroxicam, diclofenac, indomethacin, and etoricoxib [5, 8].
    a. **Naproxen:** It is a nonselective COX inhibitor having a stronger anti-inflammatory activity and potent in inhibiting leucocyte migration. Peak anti-inflammatory effect starts after 2–4 weeks.
        i. Pharmacokinetics: It is absorbed in fullest extent after oral administration and is absorbed slowly via rectal route. It is 99% plasma protein bound with a variable $t_{1/2}$. With advancement of age, the renal function declines, and the $t_{1/2}$ increases. It is 30% metabolized in liver, and its excretion occurs via urine. It crosses placenta and is also excreted in milk.
        ii. Dosage: It is started in a dosage of 750 mg stat followed by 250 mg twice or thrice daily.
        iii. Adverse effects: These are mostly gastrointestinal in nature like heartburn, nausea, dyspepsia, abdominal pain, constipation, diarrhea, and stomatitis. CNS side effects like headache, drowsiness, headache,

dizziness, and vertigo and other adverse effects like pruritis, diaphoresis, loss of renal function, angioedema, and thrombocytopenia can also occur. Reports also suggest that it can also increase the risk of myocardial infarction [8].

b. **Piroxicam**: Another nonselective COX inhibitor having a potent anti-inflammatory action and longer duration of action. In addition to inhibition of COX enzyme, it has also been proposed to inhibit neutrophil activation and inhibition of proteoglycanase and collagenase in cartilage.

   i. Pharmacokinetics: Completely absorbed upon oral administration and undergoes enterohepatic circulation. It is 99% protein bound and is metabolized in the liver by CYP2C9. t1/2 is approximately between 15 and 20 hours. Steady state plasma concentrations are attained in 7–12 days and further excreted in urine and feces.

   ii. Dosage: It is given in a dose of 20 mg daily.

   iii. Adverse effects: Experienced by 20% of the patients and eventually 5% of the recipients discontinue the treatment. The adverse effects are similar to those of naproxen though more in intensity. It is not a first-line agent for treatment of pain and inflammation in gout among all NSAIDs [9].

c. **Indomethacin**: A potent nonselective COX inhibitor. It also inhibits motility of polymorphonuclear lymphocytes, inhibits synthesis of mucopolysaccharides, and has a direct COX-independent vasoconstrictor effect.

   i. Pharmacokinetics: It has a good bioavailability after oral administration. Peak plasma concentrations are achieved within 1–2 hours. It is 99% plasma protein bound, and concentration within the synovial fluid equals that of plasma concentration in 5 hours of oral administration. It also undergoes enterohepatic circulation due to which it has a variable t1/2 and averages out to be about 2 hours.

   ii. Dosage: It is given in a dose of 25 mg twice of thrice daily or 75–100 mg at night.

   iii. Adverse effects: Experienced by majority of patients but in particular elderly. The gastrointestinal adverse effects are similar as that of naproxen though it can also cause ulcerations within the bowel. Certain CNS adverse effects like headache, dizziness, vertigo, and mental confusion can also occur. It should be prescribed cautiously to patients with epilepsy, psychiatric disorders or Parkinson's disease as they are at more risk of eliciting serious CNS side effects. It can also cause certain hematopoietic disorders like neutropenia, thrombocytopenia, and rarely aplastic anemia. Probenecid increases the plasma concentration of indomethacin, so the dose should be lowered in such case [10].

d. **Etoricoxib**: It is a newer selective COX-2 inhibitor having the highest COX-2-selective activity. It is given only in patients with high risk of peptic ulcer, perforation, or bleeding.

i. Pharmacokinetics: It is incompletely absorbed, has a longer t1/2 between 20 and 60 hours, metabolized in the liver, and excreted via urine. Hepatic impairment promotes its accumulation in the body, whereas renal impairment does not.

ii. Dosage: It is given in a dosage of 60–120 mg once daily.

iii. Adverse effects: Dyspepsia, abdominal pain, pedal edema, rise in BP, dry mouth, aphthous ulcers, taste disturbance, and paresthesias. It should not be used in patients with or at risk of cardiovascular or cerebrovascular disease as it can cause prothrombotic events [9].

2. **Colchicine**: It is one of the oldest drugs available for treatment of acute gout. An alkaloid obtained from *Colchicum autumnale* having no analgesic or anti-inflammatory property nor having any effect on inhibiting synthesis or increasing excretion of uric acid. It is not used as a first-line drug due to its narrow therapeutic window and increased side effects. It suppress gouty inflammation by various mechanisms: It (a) prevents granulocyte migration into the inflamed joint, (b) inhibits release of glycoprotein which causes aggravates inflammation by forming lactic acid and by releasing lysosomal enzymes which lead to joint destruction, and (c) binds to an intracellular protein called tubulin and causes depolymerization and disappearance of microtubules in granulocytes. Collectively, these prevent migration of granulocytes into the area of inflammation and further prevent it. It also limits monosodium urate crystal-induced NALP3 inflammasome activation and subsequent formation of IL-1β and IL-18. It exerts various other actions also like lowering of body temperature, increased sensitivity to central depressants, and depression of respiratory center. Colchicine is also used in management of chronic gout as bridging therapy with uric acid synthesis inhibitors to prevent development of symptoms of acute gouty arthritis initially due to mobilization of urate from tissues.

a. **Pharmacokinetics**: It has a rapid but variable absorption via oral route with no effect of food on its absorption. It achieves peak plasma concentrations within 0.5–2 hours. It is 39% plasma protein bound; larger volume of distribution due to formation of colchicine-tubulin complexes with different tissues and undergoes enterohepatic circulation accounting for its longer t1/2, i.e., 31 hours. It is metabolized mainly by oxidative demethylation with the help of enzyme CYP3A4. Approximately 40–65% of colchicine is excreted unchanged in urine, and the main organs with high colchicine concentration are the kidney, spleen, and liver sparing the heart, skeletal muscles, and brain. Colchicine acts as a substrate for P-glycoprotein efflux and is contraindicated in patients with hepatic or renal impairment already on CYP3A4 or P-glycoprotein inhibitor therapy.

b. **Dosage**: Individualization needs to be performed as per the age, renal/hepatic function, and concomitant medications and is administered only by oral route. A gap of 7–14 days should be present between courses of gout treatment with colchicine therapy to avoid accumulation of drug and further toxicity. Patients suffering from cardiac, hepatic, or renal disease are better off with NSAIDs or glucocorticoids. For the treatment of acute gout flare, two tablets 0.6 mg each should be taken first followed by a single 0.6 mg tablet after 1 hour. Pain, swelling, and redness subside within 12 hours and are resolved by 48–72 hours.

For prophylaxis in patients with recurrent gout having less than one attack per year, 0.6 mg tablet is to be taken 3 or 4 days per week; those having more than 1 attack per year, 0.6 mg tablet is to be taken daily; and those having severe attacks, 0.6 mg tablets are to be taken twice daily. Caution is to be taken in patients with hepatic or renal mutilation as the drug cannot be removed by hemodialysis.

c. **Adverse effects**: The most common adverse effects are gastrointestinal (nausea, vomiting, diarrhea, and abdominal pain) as the drug undergoes enterohepatic circulation and is in constant state of contact with gastric mucosa. It is advised to stop the drug on emergence of these symptoms. Other adverse effects include myelosuppression, leucopenia, granulocytopenia, neutropenia, aplastic anemia, and rhabdomyolysis [3–5, 11].

3. **Corticosteroids**: They provide symptomatic relief to a patient of acute gout during attacks and prevent further attacks by their anti-inflammatory action. They are mostly indicated in patients who cannot be prescribed NSAIDs and colchicine. Glucocorticoids provide their anti-inflammatory effect by various mechanisms: (a) induce production of lipocortin which inhibits phospholipase A2 and decreases production of arachidonic acid leading to decrease in synthesis of inflammatory mediators like prostaglandins, leukotrienes, and platelet-activating factor; (b) inhibit synthesis and release of cytokines (IL-1, IL-4, IL-6, and TNF-α) with reduced activation of T cells and fibroblast proliferation, thereby reducing process of chemotaxis; and (c) inhibit pro-inflammatory transcription factors like nuclear factor-κB and activating protein which leads to decreased enhancement of transcription of genes for COX-2, cytokines, and nitric oxide synthase (iNOS). The drugs used are prednisolone, methylprednisolone, and triamcinolone with the advantage of being given by oral route, intravenous route, or intra-articular administration.

   a. Pharmacokinetics: All these three have an intermediate duration of action (12–36 hours). They are 90% plasma protein bound. They mainly bind to corticosteroid-binding globulin. They are metabolized both at hepatic and extrahepatic sites.

   b. Dosage: Prednisolone is given in a dose of 40–60 mg per day orally or 40 mg per day intravenously. They are given at the initial dose for 2–5 days and then tapered over 7–10 days. Triamcinolone is given intra-articularly at a dose of 10–40 mg depending on the size of the joint. They should be taken early morning so as to have less effect of hypothalamic-pituitary axis suppression.

   c. Adverse effects: They are an extension of their pharmacological actions seen with extended therapy. The adverse effects include altered distribution of fat throughout the body, edema, hypokalemia, hypertension, suppression of hypothalamic-pituitary axis, osteoporosis, hyperglycemia, peptic ulcer, cataract formation, glaucoma, myopathy, muscle wasting, susceptibility to infections, and central nervous system (CNS) side effects like psychiatric disturbances, acne, weight gain, and hyperlipidemia [4, 12].

5.2.2 For chronic gout

1. **Uricosurics**: These are drugs which favor excretion of uric acid from the body.

a. **Probenecid**: It is a highly lipid-soluble benzoic acid derivative. It mainly acts by inhibiting transport of organic acids across the epithelial barrier. Reabsorption of uric acid is inhibited by its action on the organic anion transporters (OAT) mainly urate transporter-1 (URAT-1). In addition, it also hampers pharmacokinetic properties of many other drugs also, i.e., retards tubular secretion of methotrexate and active metabolite of clofibrate, inhibits renal secretion of inactive glucuronide metabolites of naproxen, ketoprofen, and indomethacin thereby increasing their plasma concentration, hampers transport of drugs such as penicillin G, and raises the plasma levels of β lactam.

   i. Pharmacokinetics: Complete absorption occurs after oral administration and attains peak plasma concentrations within 2–4 hours. It has a dose-dependent $t_{1/2}$ and varies between less than 5 to more than 8 hours. It is 85–95% bound to plasma albumin, and the unbound part is excreted by glomerular filtration and active tubular secretion.

   ii. Dosage: Initially it is given in a dose of 250 mg twice daily and increased over 1–2 weeks to 500–1000 mg twice daily. Patient should be advised to increase the daily water intake to prevent formation of renal stones as probenecid increases urinary urate levels. De-escalation is to be started after 6 months of treatment if the uric acid levels are favorable.

   iii. Adverse effects: Mild gastrointestinal irritation is mostly seen and that too with higher doses. It should be avoided in patients with creatinine clearance 50 ml/min and is also ineffective in these patients. Overdosage leads to CNS stimulation, convulsions, and death due to respiratory failure. It is contraindicated in patients with history of renal stones [13, 14].

b. **Sulfinpyrazone**: It has neither analgesic nor neither anti-inflammatory property. It inhibits tubular reabsorption of uric acid. Due to its higher incidence of gastric irritation and other side effects, it is not used nowadays [15].

c. **Benzbromarone**: It is a reversible urate anion exchanger inhibitor present in the proximal tubule. It has not been approved by the United States (US) Food and Drug Administration (FDA) due to its risk of causing severe hepatotoxicity; however, it is used as a potent uricosuric in certain Southeast Asian countries [16].

d. **Lesinurad**: Another uricosuric which has been approved for use in combination therapy with a xanthine oxidase inhibitor. It acts by inhibiting the transporters URAT-1 and OAT-4 and decreasing reabsorption of uric acid.

   i. Pharmacokinetics: It has a fast oral absorption showing 100% availability and is largely plasma protein bound. It has a t1/2 of 5 hours, metabolized by CYP2C9, and is excreted in urine and feces.

   ii. Dosage: Given at a dosage of 200 mg per day along with a xanthine oxidase inhibitor. It should not be used in patients with creatinine clearance 45 ml/min.

iii. Adverse effects: Black box warning has been issued by the US FDA against its use as monotherapy due to risk of causing acute renal failure. It has also propensity to cause an increase in serum creatinine levels. Other adverse effects like headache and gastritis can also occur. Interruption with xanthine oxidase inhibitor requires stoppage of lesinurad also [14].

2. **Uric acid synthesis inhibitors (Xanthine oxidase inhibitors)**

a. **Allopurinol**: This compound was initially produced as an antineoplastic agent and was later found to lack that property. Later it was found to have xanthine oxidase enzyme-inhibiting property. Xanthine oxidase enzyme is responsible for conversion of hypoxanthine and xanthine into urate, and by inhibiting this enzyme, allopurinol prevents formation of urate. Allopurinol in low concentrations acts as a competitive and as a noncompetitive inhibitor at high concentrations of xanthine oxidase enzyme. The formation of oxypurinol (alloxanthine), its primary metabolite, and its long perseverance in tissues is majorly responsible for its activity. Oxypurinol inhibits the reduced form of xanthine oxidase enzyme. Conversion of hypoxanthine to xanthine takes place in the presence of xanthine oxidase enzyme which is also blocked by allopurinol (inhibition of de novo purine synthesis). The purines are mainly excreted by the kidney. In the absence of allopurinol, the major purine excreted is uric acid, whereas it is hypoxanthine, xanthine, and uric acid in the presence of allopurinol. This treatment leads to excess purine load in the kidney which might lead to a risk of xanthine stones which can be minimized by increasing the fluid intake and alkalization of urine. It also helps in dissolution of tophi and decreases the chances of development and progression of chronic gouty arthritis. It also prevents development of nephropathy by preventing formation of uric acid stones; however, it cannot restore the renal function after injury to the renal tissue has occurred, but it may retard the progression. Initially on starting the therapy, chances of acute attack of gouty arthritis increase due to movement of uric acid outside from the tissues, and this can be concealed by giving NSAIDs and colchicine along with allopurinol. Allopurinol is also used in patients undergoing chemotherapy for hematological malignancies to prevent hyperuricemia and consequently gout.

i. Pharmacokinetics: It has a fast oral absorption with peak plasma concentrations achieved in 60–90 min. Plasma half-life of allopurinol is 1–2 hours and that of oxypurinol is 18–30 hours which allows for once daily dosing. It undergoes metabolism which leads to formation of its metabolite oxypurinol. Around 20% of unabsorbed drug is excreted in feces within 48–72 hours, and other 10–30% of unabsorbed drug is excreted in urine. It is not bound to any plasma protein and is distributed in total tissue water except the brain. Oxypurinol is excreted via glomerular filtration.

ii. Dosage: It can be given both as an oral and intravenous preparation. The main aim of treatment is to decrease the uric acid level to 6 mg/dl. The drug is initially started at 100 mg/day for patients with glomerular filtration >40 mg/min and is increased by 100 mg weekly. It is usually given in once daily dosing, but dosing above 300 mg should be divided accordingly. Dosage in patients with reduced glomerular filtration (<40 mg/min) should be less than that of a normal person (>60 mg/min).

iii. Adverse effects: It is generally well tolerated. However, the most common adverse effects are hypersensitivity reactions which are seen after months and years of treatment, and this can further precipitate into serious reactions if the drug is not stopped. The cutaneous reactions seen are mainly pruritic, erythematous, or maculopapular eruption. It is contraindicated in patients who previously have experienced serious reactions with it, in nursing mothers and in children except those with malignancy and inborn errors of metabolism. It increases half-life of probenecid and enhances its uricosuric effect; on the other hand, probenecid increases clearance of oxypurinol, thereby increasing the dose required. Allopurinol also inhibits enzymatic activation of mercaptopurine and azathioprine by xanthine oxidase enzyme which should be kept in mind in patients undergoing chemotherapy. It also increases risk of bone marrow suppression if given with cytotoxic drugs and interferes with metabolic inactivation of some drugs like warfarin.

b. **Febuxostat**: Another xanthine oxidase inhibitor which has been approved for treatment of hyperuricemia in gout though it is not recommended for treatment of asymptomatic hyperuricemia, having the advantage of being more potent, selective, no dose reduction in renal disease patients, and less chances of causing allergic reactions. Febuxostat is used in conditions when patient is intolerant to allopurinol or when it is contraindicated. It is a non-purine inhibitor of xanthine oxidase enzyme inhibiting both reduced and oxidized forms of the enzyme. It usually requires concurrent treatment with NSAIDs or colchicine.

i. Pharmacokinetics: It has a rapid absorption with peak plasma concentrations being achieved after 1–1.5 hours of drug intake. The half-life is around 5–8 hours and is metabolized both by conjugation by UGT enzymes (UGT1A1, UGT1A3, UGT1A9, and UGT2B7) and oxidized by CYP enzymes (CYP1A2, CYP2C8, CYP2C9) and non-CYP enzymes indicating possibility of drug-drug interactions. It is excreted by both hepatic and renal routes. No dose reduction is required in case of mild to moderate hepatic or renal impairment.

ii. Dosage: It is initiated at 40 mg/day and is increased as per the patient's uric acid levels.

iii. Adverse effects: The most common adverse effect seen with it is abnormality with liver function tests, nausea, joint pain, and rash, so regular monitoring of liver function is required. It can also cause an increase in gout flares as during the therapy there is mobilization of urate crystals from the tissue deposits due to a decrease in the uric acid levels. Patients should also be regularly checked for any cardiovascular complications. Drug levels of theophylline, mercaptopurine, and azathioprine, which are metabolized by xanthine oxidase enzyme, are increased if given with febuxostat and febuxostat and are contraindicated in patients taking azathioprine or mercaptopurine.

3. **Uricase**: It is an enzyme which is present in birds which converts uric acid into soluble allantoin which is easily excreted.

a. **Rasburicase**: A recombinant uricase which has been shown to lower urate levels much efficiently than allopurinol. It has been indicated as the initial management for elevated uric acid levels in children and adults suffering from leukemia, lymphoma, and solid tumor malignancies and undergoing chemotherapy leading to significant hyperuricemia. However, there are certain limitations with it like formations of antibodies against it.

   i. Dosage: It is given as 0.2 mg/kg IV as infusion over 30 minutes every day up to 5 days.

   ii. Adverse effects: Certain adverse effects like nausea, headache, constipation, diarrhea, hemolysis in glucose-6-phosphate dehydrogenase (G6PD) deficient patients, methemoglobinemia, acute renal failure, and anaphylaxis are seen with it.

b. **Pegloticase**: It is pegylated uricase converting uric acid into soluble allantoin. It is used for the treatment of severe, treatment refractory, chronic gout or when other urate-lowering therapies are contraindicated. Problem of development of antibodies against it is seen with pegloticase also.

   i. Dosage: It is administered at 8 mg every 2 weeks as an infusion.

   ii. Adverse effects: Vomiting, nausea, chest pain, constipation, diarrhea, erythema, pruritis, urticaria, hemolysis in G6PD deficient patients, and anaphylaxis are certain adverse effects seen with it. Black box warning has been issued by US FDA against pegloticase which advises that the drug should only be administered in health-care settings and only by health-care professionals to manage anaphylactic reactions and other serious reactions [11, 17].

6. Recent developments

a. **Arhalofenate:** It has been synthesized showing a dual mechanism of action but is still pending in approval. It acts as a partial agonist to peroxisome proliferator-activated receptor-γ (PPAR-γ) and inhibits expression of IL-1, thereby inhibiting renal absorption of uric acid in the kidney by URAT-1, OAT-4, and OAT-10 transporters [18].It was initially synthesized as a drug for the management of type 2 diabetes mellitus but was also found to have anti-flare and uricosuric property. Its phase II study has been completed showing positive results, and further results from ongoing studies are awaited [19].

b. **Interleukin-1 inhibitors (anakinra, canakinumab, rilonacept):** These prevent attraction of neutrophils at the joint site. The drugs in this class are anakinra, an interleukin-1 receptor antagonist; canakinumab, a monoclonal antibody against interleukin-1 beta; and rilonacept, a chimera constituting of IgG domains and extracellular components of interleukin-1 receptor. All these have been shown to have efficacy in acute gout but still have not been approved by the drug regulatory authorities [7]. However, these are approved for their use in other diseases like rheumatoid arthritis and cryptoporphyrin-associated periodic syndrome. They are contraindicated in patients with previous hypersensitivity reactions to these drugs and any serious active infection. Further application concomitant

live attenuated vaccine is to be avoided. Concern of immunosuppression with their use has been an important reason for their disapproval [20].

c. **Verinurad:** It is also a uricosuric which inhibits the reabsorption of uric acid by acting on the URAT-1. It has been shown to be 3 times more potent than benzbromarone and 100 times more potent than probenecid and has completed phase II clinical trial.

d. **Tranilast:** It is a moderately sedative H1 anihistaminic drug, which is used in management of bronchial asthma and other allergic conditions in Japan. It has also been shown to reduce serum uric acid levels by inhibition of URAT-1 transporter and promoting excretion of urate. In addition, it has also been shown to decrease the inflammation induced by monosodium crystals in vivo by reducing leukocyte infiltration and plasma extravasation similar to colchicine and indomethacin, thereby causing flare reduction. It has completed its phase II clinical trial.

e. **Levotofisopam:** It is an S-enantiomer of racemic tofisopam which is a benzodiazepine derivative which has been approved in the United States for the management of anxiety. Phase I clinical trial has been completed, phase II studies are underway, and results are awaited.

f. **Topiroxostat:** It is a selective xanthine oxidase inhibitor. Its mechanism of action is different from that of febuxostat such that it acts as a hybrid inhibitor. It not only acts as a chemical structure based xanthine oxidase enzyme inhibition but also covalently binds to molybdenum in the active center during the hydroxylation process of the enzyme. The pharmacokinetics of topiroxostat is unaltered by mild to moderate renal impairment. It has a half-life of around 20 hours, and enzyme activity takes time to recover even after the drug has been metabolized. In patients with concurrent moderate renal impairment and hyperuricemia, a fall in serum urate and albumin levels has been reported. It has been approved by the Pharmaceuticals and Medical Devices Agency, in Japan in the year 2013, in a dose of 20–80 mg twice daily.

g. **Ulodesine:** It acts by inhibiting purine nucleotide phosphorylase (PNP) which is an enzyme that acts one-step before xanthine oxidase in production of urate. Initial concerns were shown due to inhibition of PNP enzyme due to its absence in immunodeficient patients and in patients suffering from immunologic disorders, but nothing has been reported in studies until date. Phase II studies have been completed, and further studies are awaited [19].

We all authors share the opinion that therapy of the chronic tophaceous gout is still far from optimal. Despite availability of several agents, none has been considered as ideal due either to their undesirable adverse effects profile, limited utility in patients of renal impairment, inadequate response or failure to reverse existing osseous lesions, and dissolution of tophi from the tissues. We anticipate that newer drugs that are being developed with different mechanism of actions might address these issues, but only time will prove their worth.

7. Conclusions

Gout is a metabolic disorder due to the rise in uric acid levels in the body leading to development of gouty arthritis. Its management requires both pharmacological

and non-pharmacological intervention. Newer drugs targeting various inflammatory mediators, enzymes, or transporters are in different phases of clinical development. Until date, none has reached to phase III and yet to get an approval from regulatory bodies. The quest for an optimally designed drug with desirable efficacy and acceptable safety profile is still on.

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Acronyms and abbreviations

CNS	central nervous system
COX	cyclooxygenase
G6PD	glucose-6-phosphate dehydrogenase
IL	interleukin
iNOS	nitric oxide synthase
NSAIDs	nonsteroidal anti-inflammatory drugs
OAT	organic anion transporters
PNP	purine nucleotide phosphorylase
t1/2	half-life
TNF	tumor necrosis factor
URAT	urate transporter

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Author details

Rajit Sahai, Pramod Kumar Sharma*, Arup Misra and Siddhartha Dutta
Department of Pharmacology, All India Institute of Medical Sciences, Jodhpur, India

*Address all correspondence to: pramod309@gmail.com

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