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SPECIAL EDITORIAL REVIEW

Gout: an Asia-Pacific update

Binoy J. PAUL and Reeta JAMES

Department of General Medicine, KMCT Medical College, Calicut, Kerala, India

Abstract

Even though, Hippocrates recognized gout as an affection of older men and a product of high living long back in 5th century BC, this painful condition promises to accompany humanity to the 21st century. The incidence is progressively rising and females are also affected in the modern era. There are also regional and ethnic variations in the incidence, the genetics of which is being studied. The recommended best therapy for the acute attacks and long term prophylaxis has improved remarkably in the recent years. However, patients are often treated inadequately and risk factors for their disease are not well explored in daily practice. Although well designed long term studies of current and newer treatment are welcomed, educating doctors especially the primary care physicians who manage majority of gout cases, in optimizing the currently available management options would improve the present care.

Key words: disease aetiology and pathogenesis – human, gout, metabolic and crystal arthropathies drug treatment, metabolic and crystal arthropathies epidemiology, metabolic and crystal arthropathies inflammasome.

'Screw up the vice as tightly as possible – you have rheumatism, give it another turn and that is gout' – Anonymous

Gout is one of the oldest joint diseases known to humanity. However, it is an easily misdiagnosed arthritis even in the modern era. The term gout originated from the word 'gutta' meaning a drop (in Latin), as the ancient belief was that the devil is causing the disease by instilling the poisonous humor into the joint of the victim drop by drop.[1] The Father of Medicine, Hippocrates, described many important clinical features of this disease way back in the fifth century BC which is now popular as 'Aphorisms of Gout'.[2] He said that 'Eunuchs do not take gout, nor become bald. A woman does not take gout unless her menses be stopped, A young man does not take gout unless he indulges in coitus. In gouty affection, inflammation subsides in 40 days'. Antony Van Leeuwenhoek microscopically demonstrated the needle-shaped uric acid crystals in 1679. In 1848, Sir Alfred Garrod established that elevated uric acid is the cause of gout.[3] McCarty and Hollander in 1969 proved the association between acute arthritis in gout and deposition of uric acid crystals in the joints.[4]

When serum urate concentrations persistently remain above the physiological saturation threshold of urate (around 7.0 mg/dL), monosodium urate (MSU) crystals get deposited into the joints or soft tissues such as cartilage or renal parenchyma, causing the clinical syndrome of gout. The disease often runs in families[5] but the genetic basis of gout is not well understood. Twenty-eight genetic loci are associated with serum urate levels in Europeans but newer loci have also been detected in recent studies.[6] The major gout-causing genes identified are *SLC2A9* and *ABCG2*, the urate transport genes and *SLC17A1*, which encodes sodium-dependent phosphate transporter 1, a renal transporter of uric acid.[7]

Gout often presents as severe monoarthritis of acute onset in lower limb joints such as the first metatarsophalangeal (MTP) joint or ankle. The arthritis may

Correspondence: Dr. Reeta James, Asst Professor, Department of General Medicine, KMCT Medical College, Manassery PO Mukkom, Calicut- 673602 Kerala, India.
Email: reetajames@gmail.com

subside completely but often recurs. Patients with recurrent gouty arthritis for more than 10–12 years may develop tophi in the cartilage, tendon or other soft tissues. The incidence of gout in developing countries like India is on the rise.[8] Lifestyle changes leading to reduced physical activity, obesity, protein-rich diet, alcoholism, use of drugs like thiazide diuretics, are likely causes for this increasing incidence.[3] As estrogen has good uricosuric action, gout is uncommon in females before menopause. However, increasing longevity after menopause, increasing numbers of hysterectomies, changes in the lifestyle of women and widespread use of drugs causing hyperuricemia are all causing increasing numbers of gout cases in females today.[9]

EPIDEMIOLOGY

There is a wide variation in the prevalence of gout in various populations in the Asia-Pacific region. The ethnic groups in Malaysia and China such as Malays and Tamils have higher uric acid levels compared to the other Asian populations.[10] In comparison with Caucasians, Japanese have much lower uric acid levels. People in Thailand also have very low prevalence of gouty arthritis.[11]

The highest frequency of gout in the world is reported from the modern Pacific Islander populations.[12] Both Maori and European males in New Zealand have very high prevalences of gout.[13] Compared to European females, Polynesian women have much higher serum urate levels.[14] Recently, high frequencies of renal urate transporter *SLC2A9* haplotypes (GLUT9) associated with susceptibility to gout have been reported in modern Māori and Pacific Islanders in New Zealand.[15] This genetic abnormality causes marked reduction in uric acid excretion, leading to gout. For example, in spite of very low alcohol consumption in Pukapuka in the Cook Islands, prevalence of gouty arthritis is second only to the male population of Maoris of New Zealand.[16] Unlike *SLC2A9*, *ABCG2* is found to have a strong effect only in people of western Polynesian ancestry.[17]

In Taiwan, non-aboriginals have much lower prevalence of gout compared to the aboriginal population (0.3% compared to 9.1%).[18] Taiwan is one of the countries with the highest prevalence of gout worldwide. Taiwanese aborigines have very high prevalence of gout which is shared with their genetically related Polynesian cousins, the Maori and indigenous Oceania - Pacific Islander populations. Linguistic, archaeological and genetic evidence suggest that the insular populations across the Pacific region, including Polynesians, Micronesians, Melanesians and Taiwan aborigines, are part of an Austronesian population. The ancestral homeland of Austronesians was the agricultural heartland of Southeast Asia, from where they first radiated to Formosa/Taiwan (4000 BC), then western Polynesia (1200 BC), central Polynesia (200 BC), and New Zealand (800 AD).[19] The prevalence of gout among the various Austronesian populations in these areas is very high compared to their European or other non-Austronesian counterparts in the same countries (Table 1).

Table 1 Prevalence of gout in Austronesian males[20,21]

Population	Gout %
Maori – New Zealand	10.4–13.9
Pukupuka – Cook Islands	5.3
Guam, Chammoros – Micronesia	5.3
Nauru – Micronesia	6.9
Aborigines – Taiwan	9.1
Indonesians	7.0

In comparison to European populations, uric acid levels in the blood are quite high in certain ethnic groups like Togans, Papuans and Hawaiians, but the occurrence of gout is negligible in these people.[16] The factors protecting these populations from arthritis is not yet known.

In a study conducted in South India, it was found that females had a later onset, longer duration and higher uric acid levels when compared to males. Polyarticular gout was more frequent in the elderly and females, with a greater association with tophi, renal calculi, renal dysfunction and ischemic heart disease. Hypertension, diabetes and obesity were more frequent in oligoarticular gout.[8]

In a study from Taiwan, 25% of the study population had disease onset below the age of 30 years.[22] A study from southern India revealed that almost 18% of patients with gout belong to a younger age group, that is, below 30 years. This subset is characterized by acute intermittent polyarthritis, paucity of podagra and early tophi formation.[23]

In a study from North Kerala, findings were comparable to that of other Indian studies on gout with a definite male preponderance. Initial presentation was predominantly monoarticular with the ankle joint being the commonest to be involved.[3] But overall, the first MTP joint was the commonest joint affected with > 90% having this joint involvement at some point of the disease. Most patients were under-secretors of uric acid with higher incidence of renal calculi.[3]

PATHOGENESIS

The pathological hallmark of a gout attack is the considerable neutrophil influx into the synovium and joint fluid.[24] However, since neutrophils are sparse in the normal joint, the primary event following precipitation of MSU within the joint is believed to be the interaction of MSU crystals with resident joint cells, principally the synovial lining cells, which in turn trigger neutrophil ingress. The exposure of monocyte cell lines to MSU crystals leads to the production of proinflammatory cytokines, in particular interleukin (IL)-1β,[25] and it is now understood that phagocytosis of MSU crystals is central to this process. MSU crystals may act as a 'danger' signal to cells in a similar way to microbial pathogens[26] and are phagocytosed by the macrophages, thereby triggering the formation of inflammosomes. The inflammasomes are critical in sensing MSU deposition and subsequent activation of the immune response.[27] Inflammasomes are multimeric cytoplasmic protein complexes which act as molecular platforms for the activation of inflammatory caspases following stimulation by foreign agonists.[28] The process of inflammasome assembly results in cleavage of pro-caspase-1 to produce active caspase-1, which in turn cleaves pro-IL-1β to produce IL-1β (Fig. 1). Hence, blocking IL-1 activation is coming up as a new way to treat gouty inflammation.

Higher serum levels of CC-motif chemokine ligand 2 (CCL2) and an increased percentage of circulating $CD14^+$ monocytes are seen in gout and asymptomatic hyperuricemia.[29] Hyperuricemia may initiate subclinical priming of circulating blood monocytes for adhesion and trafficking during a gout attack.[26] There is enhanced MSU crystal-induced superoxide production by neutrophils driven by the subclinical inflammatory cytokine environment combined with hyperuricemia and this contributes to elevated neutrophil IL-8 production and survival in the absence of direct crystal stimulation.[30]

DIAGNOSIS

Although the diagnosis of acute gouty arthritis is strongly suggested by a typical presentation, inflammations seen in pseudogout, calcific tendonitis, sarcoid arthropathy, serum sickness, erythema nodosum and familial Mediterranean fever may mimic the picture.[31]

The diagnosis of gout can be confirmed in an appropriate clinical setting if the joint or tophus aspirate shows needle-shaped negatively birefringent MSU crystals under compensated polarized light microscopy.[3,32] One should always exclude septic arthritis or cellulitis by Gram stain and culture of the aspirated material. When MSU crystal demonstration is not possible, typical clinical presentation with a positive family history, high serum uric acid levels and an excellent response to colchicine often establish the diagnosis. Although hyperuricemia is not a requirement for the diagnosis of gout and its presence in a patient with arthritis does not necessarily establish the diagnosis, the risk of gout increases with the degree and duration of hyperuricemia. In gout, serum and synovial fluid (SF) urate levels are significantly higher than in calcium pyrophosphate dihydrate arthritis (pseudogout), rheumatoid arthritis, septic arthritis, ankylosing spondylosis and osteoarthritis, but the serum/SF urate ratio in gout patients is lower since SF urate levels are uniquely higher than serum levels.[33] Around one-third of patients with gouty arthritis will have normal uric acid levels during the acute attack, but urate crystals can be demonstrated in the synovial fluid of these patients.[3] Diagnostic arthrocentesis during acute gout is a safe procedure with a low frequency of adverse events.[34]

Radiography in acute initial attacks may show only soft tissue swelling of the affected joint. The radiographic hallmarks of long-standing gout are those of an asymmetric inflammatory erosive arthritis often accompanied by soft tissue nodules with retention of normal joint space. Sharply punched out oval or round defects situated in the marginal area of joints often with overhanging margins are also classical of gout.[35]

Ultrasound provides a different 'sonar' picture of tophi, which may appear as hypoechoic, hyperechoic or mixed echogenicity nodules.[36] On ultrasonography (USG), MSU crystals may appear within the synovial fluid as a 'snow storm appearance' or deposit on superficial articular cartilage as the 'double contour sign'.[37] Collection of MSU crystals within tophi can also be identified by USG. Ultrasound features of MSU crystal deposition have high specificity and high positive predictive value. The specificity is also high in early disease and in absence of clinical signs of tophi.[38]

Magnetic resonance imaging (MRI) can demonstrate joint effusion, synovitis, tendon disorder, tophus, cartilage disorder or bone edema in gout.[39] Both ultrasound and MRI scanning can also image the inflammatory aspect of gouty arthopathy, including synovitis, tenosynovitis and edematous soft tissue inflammation. Evidence of increased vascularization within the synovial membrane can be obtained on power Doppler images and contrast-enhanced MRI scans.[40]

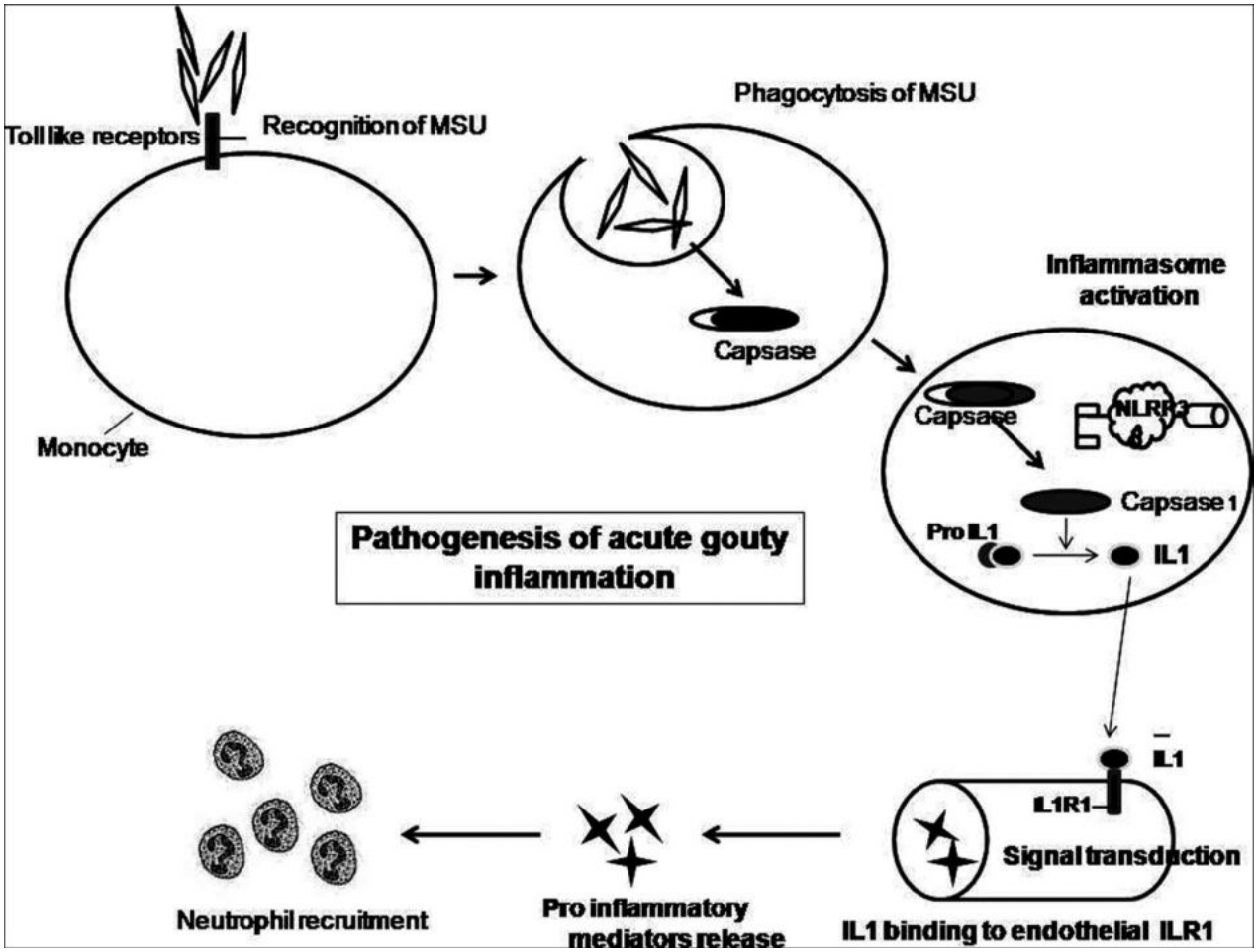

Figure 1 Pathogenesis.

Computed tomography (CT) scan may reveal discrete tophi at multiple sites adjacent to bone and within soft tissues and is helpful in scoring bone erosions.[39,41] Dual-energy CT (DECT) is an emerging area of great interest which analyzes using a 3D material decomposition algorithm that allows characterization of uric acid (allocated a specific color) to be contrasted with calcium and soft tissue (allocated other colors).[42] This means that MSU crystals can be detected with a high degree of accuracy, implying that DECT should have very high specificity for a diagnosis of gout. DECT scans detect fourfold more deposits than physical examination, indicating its potential for imaging subclinical tophi.[43]

The American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) collaborative initiative has come out with a new classification criteria.[44] For the existing ACR criteria, presence of MSU crystals alone is sufficient to fulfill criteria; they are therefore 100% sensitive by definition. The new criteria also have MSU positivity as sufficient criterion for classification, but in the absence of symptomatic urate crystals, other signs and symptoms are considered and a score of 8 or more constitutes gout.[45] Overall, the new criteria incorporates clinical, laboratory and imaging evidence and a web-based calculator makes scoring easy. Thus, the new criteria are flexible enough to enable accurate classification of gout regardless of MSU status.[45] Of all tested definitions, the 2015 ACR/EULAR criteria were found to have the best performance among survey definitions of gout (Table 2)[45] in epidemiological studies (sensitivity 92%, specificity 89%).[46]

Table 2 Comparison between old and new criteria[45]

Old criteria	New EULAR criteria
Highly subjective	Objective with clear-cut scoring pattern
Diagnosis based on presence of six or more out of 11 criteria	Diagnosis based on scoring system which can be done using web-based calculators
X-ray is the only imaging modality considered	Besides X-ray, USG and DECT are used as modalities for radiographic evidence
Urate crystals in synovial fluid are sufficient for definite diagnosis of gout	MSU in synovial fluid is a sufficient criterion, but in its absence other signs and symptoms can amount to a score enough to make a diagnosis of gout
Hyperuricemia itself is a criteria	Serum uric acid levels are subdivided into four intervals each having a different score
All joints have similar weightage	Scores differ based on the joints affected

EULAR, European League Against Rheumatism; USG, ultrasonography; DECT, dual-energy computed tomography; MSU, monosodium urate.

OUTCOME MEASURES

Until recently the outcome assessment of gout has been a neglected area of rheumatology. This has been changed significantly since gout became a topic for the Outcome Measures in Rheumatology Clinical Trials (OMERACT). Five core domains have been endorsed by OMERACT for acute gout: pain, joint swelling, joint tenderness, patient global assessmen and activity limitation.[47] The Gout Special Interest Group is trying to identify domains of interest and is now evaluating a series of outcomes for features of chronic gout, such as serum uric acid level, physical measurement or digital photography of tophi and imaging modalities.[48,49]

Gout-specific patient reported outcome instruments like the Gout Assessment Questionnaire (GAQ) were also developed that collect information about gout impact, assessing pain, well-being, productivity and treatment satisfaction. A modified version of this instrument GAQ 2.0 contains a Gout Impact Scale (GIS) and four other sections that gather clinical, background and economic data.[50] These outcome measures are definitely useful to assess the disease burden, functional disabilities, quality of life and associated comorbidities. However, the methods to measure outcomes in gout still require consensus and validation.

TREATMENT

The objectives of treatment in gouty arthritis are quick resolution of the acute attack, avoidance of further episodes and prevention of complications like renal involvement or development of tophi. The therapy includes lifestyle modification and/or drug therapy. Control of precipitating factors and comorbid illnesses like hypertension and dyslipidemia are also equally important. Lifestyle changes include weight reduction, adequate hydration, reduction or stoppage of alcohol intake, low purine diet and withdrawal of drugs causing hyperuricemia.[51] In patients on antituberculous therapy, pyrazinamide and ethambutol are found to exert hyperuricemic effect, mainly by reducing the uric acid clearance, which is reversible with no renal function impairment.[52] *SLC2A9*-mediated renal uric acid excretion is physiologically influenced by intake of simple sugars derived from sugar-sweetened beverages and hence genetic variants in *SLC2A9*, that exchange uric acid for glucose and fructose, are associated with gout (Table 3).[53,54]

The major pharmacological agents used for acute gouty arthritis include non-steroidal anti-inflammatory drugs (NSAIDs), colchicine and glucocorticoids. During acute attacks, urate-lowering therapy is better avoided as it can cause further flare-up of arthritis. If the patient is already on urate-lowering agents, the drug may be continued in the same dosage throughout the acute phase. NSAIDs are the first choice of drugs in the acute stage if the diagnosis is fairly certain. Compared to colchicines, they are better tolerated and have more

Table 3 Dietary factors in gout[54]

Dietary factors in hyperuricemia		
Protective	Causative	Neutral
Intact cow's milk	Alcohol including beer	Protein rich vegetables – legumes, beans
Vitamin C	Meat, especially organ meat	Spinach
Bing cherry	Sea foods	Mushroom
Coffee	Fructose	Nuts
Low-fat dairy products	Sugar-sweetened soft drinks	

predictable results. Indomethacin (150 mg daily) is often preferred, but other NSAIDs like naproxen or etoricoxib are also alternatively used. Colchicine is the agent of choice for treating patients in whom the diagnosis of gout is not confirmed as it is more effective in gout than in other arthritides.[31] The latest recommendation is to start colchicine at an initial dose of 1 mg orally followed by 0.5 mg after 1 h. If needed, 0.5 mg can be given after 12 h. Then continue colchicine 0.5 mg three times daily until the acute attack resolves. Colchicine being an agent with many drug interactions, the concomitant use of certain drugs may increase colchicine toxicity (Table 4).[55,56]

In patients where there is contraindication for NSAIDs or colchicine, oral or parenteral steroids are useful to relieve the pain. In resistant monoarticular involvement, intra-articular steroids are highly useful. Glucocorticoids like prednisolone 30–60 mg daily or equivalent parenteral preparations tapered over a period of 7–10 days is used in patients who are intolerant to non-salicylate NSAIDs or colchicine. Corticotropin is often used alternatively in acute gout, especially in post-surgical patients.[3] Blocking IL-1 is a novel concept in the treatment of acute gout because MSU crystals stimulate the inflammasomes leading to IL-1b secretion. IL-1 inhibitors prevent IL-1b secretion by inhibiting the inflammosome and also block IL-1 secretion by macrophages via a Toll-like receptor-dependent mechanism.[3] The anti-IL-1 drugs like anakinra,[57] canakinumab[58]and rilonacept[59] have been found to be effective in patients with acute gout (Table 5). However, they are extremely expensive when compared to the traditional agents and therefore their place in the management of gout is yet to be determined.

The aim of therapy in chronic gouty arthritis is persistent and long-term reduction in serum urate levels, well below the normal range (< 6 mg in non-tophaceous gout and < 5 mg in presence of tophi) to avoid further acute arthritis flares, reduce tophus formation and to prevent ongoing joint or organ damage[60] (Table 6[54]).

Table 4 Drugs that increase colchicine toxicity[55,56]

Macrolide antibiotics
Digoxin
Calcium channel blockers – diltiazem, verapamil
Amiodarone
Statins
Antifungal agents – ketoconazole, itraconazole
Protease inhibitors

The major groups of hypouricemic agents available for clinical use are of three categories:[61]

1 uricostatic drugs – allopurinol, febuxostat
2 uricosuric agents - primary uricosurics: probenecid, benzbromarone, sulfinpyrazone secondary uricosurics:[62] losartan, amlodipine, fenofibrate
3 uricolytic drugs – uricase, rasburicase, pegloticase.

The oldest and most widely available uricostatic agent is allopurinol,[3] a xanthine oxidase inhibitor. Although some studies recommend the initiation of urate-lowering drugs during an acute attack, in practice, hypouricemic agents are not started in the acute phase as flares may be precipitated by the rapid reduction in serum uric acid.[5] The chance of gout flares on initiation of allopurinol can be further reduced by initiating a lower dose of the drug (50–100 mg daily) and slowly increasing the dose. Prophylactic doses of colchicine (0.5 mg twice daily) or low-dose NSAIDs (naproxen 250 mg twice daily) for an initial 3–6 months are also highly useful to prevent acute attacks. The serum uric acid level becomes normal in 4 weeks in most patients and acute attacks cease completely in 6 months of continuous treatment. Reduction or disappearance of tophi may take months or years. The majority of patients require a dose of 200–300 mg daily, but occasionally 600–800 mg may be needed to keep serum uric acid at optimum levels. The important adverse effects of allopurinol are skin rashes and hypersensitivity reaction, including Steven Johnson syndrome which are more common in patients who are sensitive to sulphonamides or concomitantly taking ampicillin or thiazide diuretics.

Febuxostat[3] is a nonpurine xanthine oxidase inhibitor with high oral absorption. It is metabolized by the liver and renal excretion is insignificant. It selectively inhibits both oxidized and reduced forms of xanthine oxidase without inhibiting other enzymes in purine metabolism. The major adverse effects of febuxostat are hepatic transaminase elevation, nausea and dizziness. It is contraindicated in patients treated with azathioprine, mercaptopurine or theophylline which are metabolized by xanthine oxidase. The initial dose of febuxostat is 40 mg daily taken with or without food. If the target serum uric acid level is not achieved, dosage may be increased to 80 mg and then to 120 mg/day. Like allopurinol, the drug should be started after subsidence of an acute attack of gout and prophylactic therapy with low-dose colchicine or an NSAID is required to reduce the incidence of paradoxical gout flares. The drug is safe in patients with renal dysfunction and those who are

Table 5 Anti-interleukin-1 (IL-1) agents

Name	Anakinra[57]	Rilonacept[59]	Canakinumab[58]
Structure	IL-1 receptor antagonist	Dimeric fusion protein directed against IL-1	Fully humanized monoclonal antibody directed at IL-1β
Dose and route of administration	100 mg daily subcutaneous	80–120 mg weekly subcutaneously	150 mg subcutaneously
Indications	Refractory gout Juvenile Idiopathic arthritis (JIA) Adult-onset Still's disease	Refractory gout Cryopyrin-associated periodic syndromes (CAPS) Muckle-Wells syndrome	Refractory gout

sensitive to allopurinol. It is also useful in patients taking warfarin as it has no drug interaction with oral anticoagulants, unlike allopurinol. Topiroxostat and Y700[63] are other xanthine oxidase inhibitors. Topiroxostat was approved for use in Japan in June 2013.[64]

The second group of hypouricemic agents are the uricosuric agents like probenecid which is currently in limited supply in many countries. It is a useful agent in hyperuricemia induced by diuretics.[3] It should not be used in patients with nephrolithiasis or uric acid overproduction. Benzbromarone and sulfinpyrazone are not available in India. Losartan,[65] an angiotensin II receptor blocker, acts as a uricosuric agent by inhibiting urate reabsorption by renal tubules. (This does not appear to be a class effect). It also reduces hyperuricemia caused by thiazides and hence is a useful agent in hypertensive patients developing gout.[6] Amlodipine, a calcium channel blocker, at a dose of 5–10 mg/day is also found to be useful in reducing urate levels in patients with cyclosporine-induced hyperuricemia. Fenofibrate, a drug widely used for control of dyslipidemia, is also found to have moderate uricosuric action. It is useful in patients having gout and hyperlipidemia.

The other important group of hypouricemic drugs are the uricolytics which have the unique ability to convert uric acid to soluble allantoin. Uricase (urate oxidase) is present in lower animals but not in man. A biosynthesized recombinant uricase (rasburicase) is available for tumor lysis syndrome but the drug is highly antigenic. Uricase formulated with polyethylene glycol (pegloticase) is a potentially powerful agent for treating refractory gout in those who are unable to tolerate other drugs.[66] It has the advantages of prolonged half life and decreased antigenicity. It could have a role in debulking tophi in advanced gout before switching to another agent for maintenance treatment.

Lesinurad[67] is a urate transport inhibitor (inhibits URAT 1 and OAT 4 in renal tubules[47]) for treating hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with a xanthine oxidase inhibitor alone. It very recently received US Food and Drug Administration approval.

Table 6 Indications for urate lowering therapy[54]

- Patients with more than two attacks per year
- Chronic tophaceous gout
- Chronic gout associated with renal impairment or urate calculi
- Radiographic changes of gouty arthropathy
- Uric acid over-production due to purine enzyme defects
- Adjunct to cytotoxic therapy to prevent tumor lysis syndrome

EMERGING THERAPIES

In spite of optimal management, some patients develop gouty attacks. In some others, due to comorbidities or contraindications, many of the existing drugs cannot be used. Hence, there is a definite need for newer drugs (Table 7).

Lesinurad, in combination with febuxostat, shows additive urate-lowering effects.[65] Ulodesine is an oral

Table 7 Newer drugs for hyperuricemia and gout

Urate transporter (URAT1) inhibitors	Lesinurad, arhalofenate,[54] Tranilast[54]
Xanthine oxidase inhibitors	Topiroxostat, Y700
Purine nucleotide phosphorylase (PNP) inhibitors	Ulodesine[68]
Melanocortin 3 receptor agonists[68]	ʊ-MSH
Oral interleukin-1 inhibitors	AC201, caspase inhibitors
Uricosuric agents	Levotofisopam[54]

purine nucleotide phosphorylase inhibitor which blocks production of uric acid at the step higher in the purine catabolic pathway than xanthine oxidase inhibitor.[65] Ulodesine synergistically lowers serum urate when combined with allopurinol.[68] Levotofisopam is the s-enantiomer of racemic tofisopam, a benzodiazepine derivative.[68] Arhalofenate, a dual-acting anti-inflammatory and urate lowering drug, is a peroxisome-proliferator-activated receptor-alpha modulator developed for glycemic control, which is also a potent oral IL-1β inhibitor with uricosuric effects.[68] There is no observed decrement in the uricosuria of arhalofenate with decline in kidney function.[68]

Newer targets of interest seem to be the intestinal transporters of uric acid.[54] Upregulation of adenosine triphosphate-binding Cassette transporter G_2 ($ABCG_2$ exporters) in seen in chronic kidney disease where the principal burden of uric acid elimination shifts from kidney to gut. These drugs may be useful in those with risk of developing uric acid kidney stones with uricosuric agents.

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