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An Update on the Pathology and Clinical Management of Gouty Arthritis

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Abstract

Gouty arthritis is an inflammatory disease initially triggered by the deposition of monosodium urate crystals into the joint space, developing into an inflammatory cascade resulting in the secretion of several proinflammatory cytokines and neutrophil recruitment into the joint. It is associated with debilitating clinical symptoms, functional impairments, and a substantial impact on quality-of-life.

Currently available agents are generally effective but associated with a number of adverse events and contraindications that complicate their use. Increased understanding of the inflammatory pathogenesis of gouty arthritis has paved the way for development of several new agents that may provide increased efficacy and reduced toxicity.

Keywords: Chronic diseases; Inflammation; Pathophysiology

Introduction

Gout is a relatively common inflammatory condition, affecting an estimated 8.3 million individuals in the United States by 2008 [1-3]. It is more prevalent in men than women at a 4:1 ratio prior to the age of 65 years, after which it narrows to a 3:1 ratio [4]. Prevalence also increases dramatically with age, with almost 12% of males aged 70-79 years affected compared with <3% in men younger than 50 years (Figure 1) [1,2].

Given its demographics amongst the aging population, gout frequently presents with multiple comorbidities: hypertension in up to 58% of gouty patients, dyslipidemia in 45%, both hypertension and a lipid disorder in 33%, and diabetes mellitus in 20% [5]. The most frequently filled prescriptions amongst these patients include antihypertensive drugs, statins and non-steroidal anti-inflammatory drugs (NSAIDs). Therefore, gout represents a condition of the aging population where effective management can be frequently complicated by substantial comorbidities.

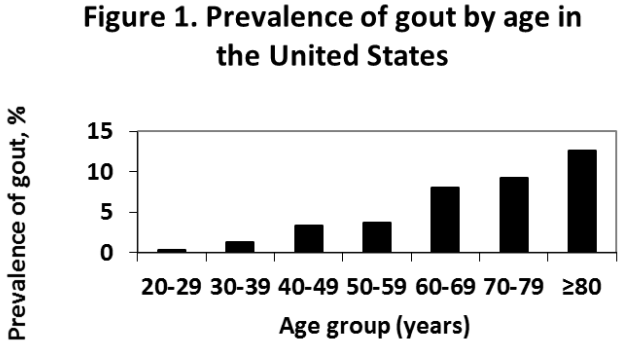

Figure 1: Prevalence of gout in the United States according to age.

Chronic hyperuricemia is a prerequisite in the development of gouty arthritis. Uric acid is a weak acid present physiologically in its ionized form as urate, and it is a product of purine breakdown which is excreted to remove nitrogenous waste [6]. Diet, biosynthesis and excretion maintain homeostasis of urate levels in the body; overproduction or, more commonly, insufficient renal clearance cause chronic hyperuricemia. This in turn leads to supersaturation of plasma urate, and at concentrations >6.8 mg/dL, monosodium urate (MSU) crystals can precipitate [7]. When MSU crystal deposits near a joint are released into the joint space causing inflammation, the result is acute gouty arthritis. However, hyperuricemia does not always lead to gouty arthritis, so other factors facilitate the process. The key inflammatory mediator in this pathway is interleukin (IL)-1ß, which therefore makes it a viable therapeutic target [8]. This review aims to summarize the current understanding of the role of IL-1ß in the inflammation seen in patients with gouty arthritis and to review recent developments in the therapeutic management of this debilitating condition.

Pathophysiology of Gouty Arthritis

In hyperuricemic patients, MSU crystal deposition into the joints triggers the inflammation which is the cause of gouty arthritis [6]. The innate immune system, which normally provides the initial non-specific immune response to invading

pathogens, launches this inflammatory reaction. Uric acid is released from injured and dying mammalian cells and macrophages in the joint space phagocytise the resulting MSU crystals (Figure 2).

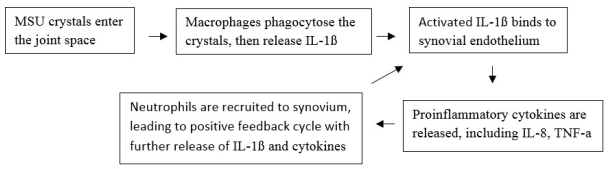

Figure 2: IL-1ß signalling leads to recruitment of neutrophils and amplification of an acute inflammatory cascade (IL-interleukin; MSU-monosodium urate; TNF-α-tumor necrosis factor alpha).

Thus, MSU crystals elicit innate immunity in a manner similar to that caused by microbial infection [9]. Within the cytosol of the macrophage, the internalization of MSU crystals then triggers the formation of a protein scaffold known as an inflammasome, a high molecular weight protein complex. The inflammasome provides a platform for Caspase-1 to process inactive pro-interleukin (IL)-1ß into biologically active IL-1ß, which is then secreted from the cell [10,11]. Macrophage activation of IL-1ß requires not only MSU crystals, but also co-stimulation with free fatty acids or lipopolysaccharide [12,13]. Since the consumption of alcohol or a large meal can increase free fatty acid concentrations and precede gouty arthritis flares, free fatty acids' role in releasing IL-1ß may be an important factor in the development of gouty arthritis flares [13].

The cell proliferation, differentiation and apoptosis in gouty arthritis are regulated by IL-1ß, the key proinflammatory cytokine that activates a variety of inflammatory mediators responsible for neutrophil influx to the synovium, a hallmark of gouty arthritis (Figure 2) [14]. Genetic knockout rodent models have demonstrated that activation of the IL-1 receptor on endothelial cells by IL-1ß is a crucial step in the development of MSU-induced inflammation. IL-1 receptor activation induces the transcription of pro-inflammatory cytokines and chemokines which generate subsequent inflammatory processes [11,15,16]. Moreover, neutrophil influx creates a positive feedback loop via further phagocytosis of MSU crystals and the perpetuation of both IL-1ß release and its associated inflammatory processes. Studies in mice have shown that strategies decreasing the level of circulating IL-1ß, including antibodies to IL-1ß and murine IL1 Trap, greatly reduce MSU-induced peritonitis [15,16].

MSU-induced inflammation in macrophages also up regulates other cytokines, including IL-6 and tumor necrosis factor (TNF-a) [16]. However, although MSU crystals stimulate the production of TNF-a from human blood monocytes and synovial cells, preliminary evidence suggests that an anti-TNF-a antibody does not prevent neutrophil infiltration in a model of MSU-induced peritonitis, suggesting that TNF-a is not a critical intermediate in the development of inflammation in gouty arthritis [17]. Likewise, in patients with gouty arthritis, therapeutic intervention targeting TNF-a has been generally unsuccessful, with only isolated reports of patients with chronic tophaceous gout responding to anti-TNF-a therapy [18].

Over time, the acute inflammation accompanying recurrent flares of gouty arthritis can culminate in pathological joint damage. Sustained accumulation of MSU crystals allows formation of tophi consisting of MSU crystals in a matrix of lipids, protein and mucopolysaccharides [19]. Tophi are also sites of production for enzymes such as matrix metalloproteinases, which can degrade bone and cartilage [20]. The tophi-bone junction also includes osteoclasts, the principal resorptive cells responsible for removal of bone tissue which contribute to bone resorption and erosion formation [21]. Another contributor to bone damage is the elevated levels of proinflammatory cytokines associated with gout flares. For example, IL-1 is a critical intermediate in the process of bone and cartilage damage, including via osteoclast formation [22]. Its key role in the processes of inflammatory cartilage and bone degradation was shown in a mouse model of TNF-mediated inflammatory joint disease, as genetic knockout of IL-1 led to a significant reduction in bone erosion and osteoclast formation.

On the other hand, expression of anti-inflammatory cytokines such as IL-37 in MSU-treated peripheral blood human macrophages inhibits production of crystal-stimulated pro-inflammatory cytokines including IL-1ß, TNF-a, and IL-6 [23]. Measurement of IL-37 protein levels in humans reveal that it is up regulated in gout flares compared to healthy controls, but also that it is even more elevated in non-acute gouty arthritis than acute gouty arthritis ($P<0.05$). But when IL-37 is silenced in these macrophages, production of pro-inflammatory cytokines increases. Thus, IL-37 represents another avenue for research of potential molecular targets in gout.

Diagnosis of Gouty Arthritis

Although the gold standard for diagnosis of gouty arthritis is the visualization of MSU crystals in synovial fluid or in fluid aspirated from a tophus, a presumptive diagnosis can be made solely on symptom presentation [24]. The combination of rapid onset of pain, swelling and tenderness in a single joint, especially when associated with a distal lower extremity joint (commonly the first metatarsophalangeal [MTP1] joint or podagra), which resolves within a few days to 2 weeks suggests a reasonably accurate presumptive diagnosis. Additional risk factors potentially indicative of gouty arthritis include a family history of gouty arthritis, the presence of urolithiasis, comorbidities such as obesity or hypertension, or the use of urate-elevating medications.

A user-friendly diagnostic rule that does not require joint fluid analysis has been developed based on logistic regression models of the characteristics most commonly associated with gout [25]. In this model, male sex, previously reported arthritis attack, onset within 1 day, joint redness, MTP1 joint involvement, hypertension or =1 cardiovascular disease and serum uric acid (SUA) levels exceeding 5.88 mg/dL were independently predictive of gout as confirmed by joint fluid analysis. Scoring these 7 variables out of a maximum of 13 points (sex=2 points;

previous attack=2 points; onset within 1 day=0.5 points; joint redness=1 point; MTP1 involvement=2.5 points; hypertension=1 points; cardiovascular disease=1.5 points and serum urate>5.88 mg/dL=3.5 points) was found to accurately predict gout. In a follow-up prospective diagnostic validation study, the diagnostic rule performed well in 390 monoarthritis patients in a secondary care setting who underwent joint fluid aspiration [26]. A score ≥ 8 yielded a positive predictive value of 0.87, while a score ≤ 4 yielded a negative predictive value of 0.95. For an intermediate score between 4 to 8, the authors continued to recommend arthrocentesis. The area under the receiver operating characteristic curve for the diagnostic rule was 0.86 (95% CI 0.82, 0.89). The Hosmer Lemeshow goodness-of-fit test revealed a non-significant difference between the expected and the observed probability (P=0.64), demonstrating a good fit.

Treatment of Gouty Arthritis

Several organizations have published guidelines for the diagnosis and management of gouty arthritis, including The European League Against Rheumatism (EULAR) [24], The American College of Rheumatology [27,28], The American College of Physicians [29] and The British Society for Rheumatology [30]. The overall management of gouty arthritis has 3 phases: controlling acute flares, controlling hyperuricemia, and prophylaxis to prevent painful recurrences (Figure 3).

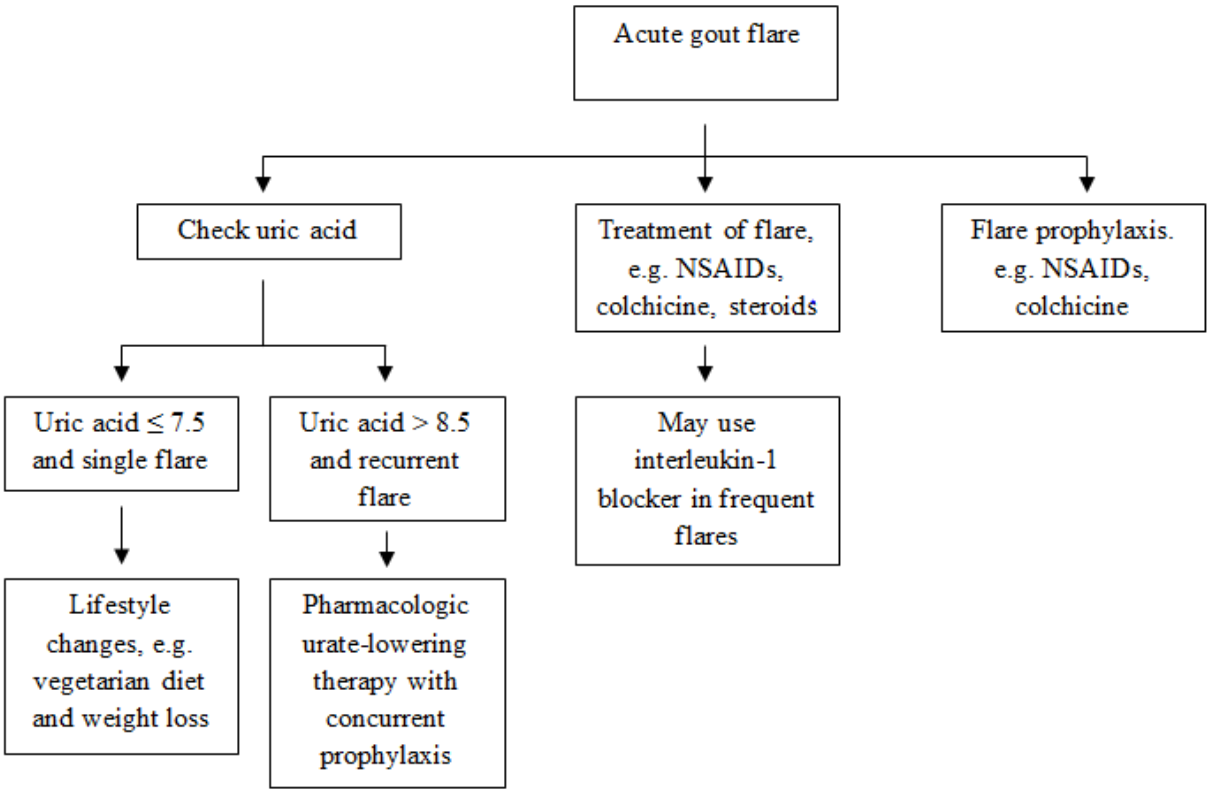

Figure 3: Overall Approach to Gout Treatment.

Acute Attack

The first-line treatment for relief of acute pain associated with flares of gouty arthritis includes NSAIDs, colchicine, systemic or intra-articular steroids, or a combination [24,27-29]. If these are contraindicated and the patient has frequent flares, then interleukin-1 blockers should be considered. Treatment duration is typically 1-3 weeks, depending on the severity of the attack and whether one or multiple joints are involved. Indomethacin and naproxen are the NSAIDs approved for use in acute gouty arthritis whilst ibuprofen and celecoxib are not approved for use in this indication. However, in clinical practice, all NSAIDS are often utilized, without substantial difference in efficacy or side effect profile. Indomethacin should be initiated at 50 mg 3 times daily until pain is tolerable, after which the dose should be rapidly reduced until complete cessation is achieved [31]. As with all NSAIDs, indomethacin is contraindicated in patients with asthma, urticaria or other allergic-type reactions, and there are warnings regarding its use in patients with cardiovascular disease, hypertension, congestive heart failure and those at risk of gastrointestinal bleeding. Recommended dosing of naproxen is 1000-1500 mg/day on day 1, followed by 1000 mg/day until the flare subsides, and sulindac is another therapeutic option which can be initiated at 200 mg twice daily [32,33]. Like indomethacin, both indomethacin and sulindac share a profile of warnings and contraindications for patients with cardiovascular disease or at risk of gastrointestinal bleeding [32]. Given the potential for gastrointestinal ulceration and bleeding, as well as the exacerbation of common co-morbidities in this patient population (e.g. renal dysfunction, hypertension), it is the opinion of these authors that the use of non-selective NSAIDs in patients over the age of 65 be avoided, particularly in the

presence of significant underlying renal dysfunction or a previous history of gastrointestinal ulceration and bleeding. During an acute attack, diet recommendations include hydration with 8-16 cups of water per day and avoidance of meat, seafood and alcohol [34].

A well-established treatment for acute gouty arthritis, colchicine received approval relatively recently from the US Food and Drug Administration for use in this indication [35]. Dosage for the prophylaxis of gout flares is 0.6 mg once or twice daily, whereas for treatment, patients should receive 1.2 mg at the first sign of a gout flare followed by 0.6 mg 1hrs later. The most frequently reported adverse event is diarrhea, colchicine is contraindicated in patients with renal or hepatic impairment, and concurrent administration of P-glycoprotein or strong CYP3A4 inhibitors should be avoided. The approval of colchicine is based on the results of the AGREE (Acute Gout Flare Receiving Colchicine Evaluation) study: a placebo-controlled, randomised, double-blind, clinical trial in 185 adult patients with a confirmed diagnosis of gouty arthritis and ≥ 2 flares in the previous 12 months, and who had an eligible gout flare within the study period [36]. Colchicine at a low (1.8 mg) or high (4.8 mg) dose administered over 6 hours were both significantly more effective than placebo, with 37.8% and 32.7% achieving a ≥ 50% reduction in pain scores within 24 hours of starting treatment, compared with 15.5% of those receiving placebo, respectively (P=.034 and P=.005 for comparison of high- and low-dose versus placebo, respectively). The most frequent adverse event amongst patients receiving colchicine was diarrhea, reported by 23% of patients receiving the low-dose (all mild-moderate) and 76.9% of those receiving the high-dose (19.2% of patients in this arm reported severe diarrhea).

Another therapeutic option for acute gout is systemic corticosteroids, and the recommended dose of oral prednisolone is 30-35 mg/day for five days [24,37]. The evidence for this comes from several randomized control trials demonstrating equivalent analgesic efficacy between oral prednisolone and naproxen, oral prednisolone and indomethacin, and oral prednisolone/paracetamol and oral indomethacin/paracetamol, respectively [38-40]. Intra-articular injection with a long-acting steroid may be effective at alleviating acute pain in one easily accessible joint [24,30].

A large number of patients with gout have contraindications to the currently available therapies, as shown in a retrospective database analysis of contraindications and prescribing practices in 807 patients with an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code diagnosis for gout [41]. There was a high prevalence of comorbidities and contraindications to gout medications; 89% of patients with gout had hypertension, 63% had hyperlipidemia, 47% had chronic kidney disease, 37% had coronary artery disease and 28.9% had diabetes. Furthermore, most patients had multiple comorbidities, with 2, 3 or 4 comorbidities present in 17%, 22% and 25% of patients, respectively. These comorbidities translated into high rates of contraindications to gout therapy. More than 90% of patients had ≥ 1 contraindication to NSAIDs, 95% had a contraindication to glucocorticoids and at least 50% had at least 1 contraindication to colchicine. In total, each patient had a mean of 3.5 contraindications to gout drugs. However, this study also revealed that contraindicated individuals often received extensive therapies for gout: 18% of patients with a contraindication to NSAIDs had received treatment with these drugs, and 41% of patients with a contraindication to colchicine had received ≥ 1 colchicine prescription. Interestingly, use of glucocorticoids was relatively rare, both amongst those with and without contraindications.

These data clearly show that a substantial proportion of patients presenting to primary practice with gout have their treatment options severely limited due to contraindications to existing therapies, particularly among elderly patients with common comorbidities associated with advancing age. This corresponds with the many factors associated with development of gout, particularly alcohol and dietary excess, which are also broadly associated with cardiovascular disease. New guidelines recommend consideration of IL-1 blockers for patients with acute gout in whom first-line treatment is contraindicated [24]. These agents exert an anti-inflammatory and analgesic effect by targeting IL-1ß, the pivotal mediator in the underlying inflammatory response seen in gouty arthritis. Clinically, the IL-1ß receptor antagonists, anakinra and rilonacept, and the fully human IL-1ß monoclonal antibody, canakinumab, have each shown considerable early promise in treating flares of gouty arthritis.

IL-1ß signalling blockade

A recombinant, non-glycosylated form of the human IL-1 receptor antagonist, anakinra is approved for use in patients with moderate to severely active rheumatoid arthritis (RA) for whom first-line therapies are not an option and neonatal-onset multisystem inflammatory disease [42]. In several small case series of up to 10 patients each, most patients developed favourable short-term responses to anakinra [43,44], including complex hospitalized patients who failed first-line treatment or had contraindications [45,46]. However, recurrent flares after discontinuation of treatment were common, occurring in 9 of 10 treated patients in one study [43]. Furthermore, a case series in which anakinra was mainly used as first-line therapy in 10 hospitalized patients showed no improvement in symptoms [47]. In a larger retrospective review of 40 patients with gout and contraindications and/or failure to at least two conventional therapies, 23 patients received anakinra for three days, seven for <15 days, and 10 for >15 days [48]. 90% patients (36/40) achieved a “good” response, median pain on a VAS scale decreased from 73.5 to 25.0, (P<0.0001), and median CRP decreased from 130.5 to 16.0 mg/l (P<0.0001). After a median follow-up of 7 months, relapse occurred in 32.5% patients (13/40), more frequently in patients not on long-term prophylactic therapy (7/10 *vs.* 6/30). Also, 6/10 of the patients on long-term anakinra developed infectious complications, which were successfully treated with antibiotics.

Rilonacept is a soluble receptor–Fc fusion protein trap for and inhibitor of IL-1a and IL-1ß, and it is approved for treatment of cryopyrin-associated periodic syndrome (CAPS) [49]. In a small proof-of-concept study of 10 patients with chronic gouty arthritis, rilonacept was associated with a significant

improvement in patient pain scores, global assessment of 'feeling well', symptom/severity adjusted scores, and a significant reduction in CRP levels compared with placebo [50]. Also, a phase III study comparing rilonacept to placebo in gout flare prophylaxis for patients on urate-lowering therapy showed decreases in gout flare frequency and duration for the rilonacept group [51]. Although injection site reactions were more common with Rilonacept, serious adverse effects and infections were similar to those for placebo. In a study of 225 patients with acute gout, however, rilonacept yielded only a non-statistically significant improvement in pain compared to indomethacin [52].

Canakinumab (ACZ885) is a human monoclonal antibody targeting the IL-1ß signaling pathway and thus suppressing its inflammatory response [53]. It has shown activity in small studies of patients with RA and CAPS, and is approved for gout flare prophylaxis and treatment of acute gout, Muckle-Wells Syndrome and familial cold auto-inflammatory syndrome. Two parallel, 12-week, phase III, double-blind, randomized control studies (β-RELIEVED and β-RELIEVED-II) compared a single 150 mg injection of canakinumab to triamcinolone acetonide placebo in treating acute gout flares in patients with contraindications and/or failure to NSAIDs or colchicine, and they were followed by 12-week extensions [54]. Compared to triamcinolone acetonide, canakinumab significantly improved VAS pain scores (−10.7 mm; P<0.0001), tenderness and swelling (ORs=2.16 and 2.74; both P ≤ 0.01), risk of flare (HR: 0.44; P ≤ 0.0001), time to first new flare (HR: 0.38; P ≤ 0.0001), and CRP levels (4.4 *vs.* 6.1 at 72 hours and 2.0 *vs.* 3.1 at 7 days, P ≤ 0.0001). But patients receiving canakinumab reported a higher rate of infections (20% *vs.* 12.2%), low neutrophil counts and thrombocytopenia [55]. A 2014 retrospective analysis pooled the data from these two phase III trials to compare canakinumab vs. triamcinolone acetonide in a novel composite response-endpoint score designed to reflect global gouty arthritis-related health outcomes [56]. Compared to triamcinolone acetonide, patients receiving canakinumab achieved a higher percentage of response criteria (65% *vs.* 49%, P<0.001) and a higher score (mean [SD]; 4.7 [2.7] *vs.* 3.7 [2.4], P<0.001), reflecting improved patient-reported outcomes and clinical markers. In another dose-ranging study of canakinumab as flare prophylaxis in 432 patients with gouty arthritis initiating allopurinol, canakinumab was associated with a decrease in flare frequency [54].

Chronic Management

Long-term therapeutic interventions should be implemented to mitigate the incidence of acute attacks in patients with recurrent flares of gouty arthritis. The overarching goal of chronic management is to reduce serum urate concentrations to below the level where MSU crystals form, through a combination of both life-style and pharmacologic strategies.

Lifestyle modification

Some experts recommend lifestyle changes for patients with gouty arthritis include healthy diet and limited alcohol intake [30], although the 2016 ACP guidelines conclude there is insufficient evidence regarding the effect of dietary changes on clinical outcomes [29]. For overweight or obese patients, weight reduction is recommended, as well as increased intake of selected foods including skimmed milk, low fat yoghurt, soy beans, vegetable protein sources and cherries [57]. On the other hand, high fructose corn syrup and high purine foods such as liver, kidney, shellfish and red meat should be discouraged [26].

Dietary recommendations are supported by large prospective studies that have examined risk factors for development of gout [58,59]. In subjects who consume seafood regularly (≥ 0.8 servings/day), the risk for gout is significantly increased (relative risk [RR], 1.51; 95% CI, 1.17–1.95) compared with those who consume seafood less regularly (0.04 servings/day). Similarly, the risk for gout is also significantly increased (RR, 1.41; 95% CI, 1.07–1.86) among regular meat eaters (2.5 servings/day) compared with those who eat less meat (0.5 servings/day) [58]. In contrast, among patients who consume a mean of 4.2 dairy servings/day (RR, 0.56; 95% CI, 0.42–0.74), the risk for gout is lower compared with those who eat less dairy product (0.5 servings/d). These findings support the use of low seafood and low meat diets for patients with gouty arthritis. In a 22-year prospective cohort study examining high fructose corn syrup in women, sugar-sweetened soft drinks increased the risk for gout by 1.74 for 1 serving per day and by 2.39 for 2 or more servings per day, while diet sodas did not increase the risk of gout [60].

In patients with gout, it is also strongly advised to reduce alcohol consumption to <21 units/week for men and <14 units per week for women. Beer, stout and port should be avoided, and patients should be encouraged to maintain 3 days each week of complete abstinence from alcohol [30]. Compared with non-drinkers, the multivariate relative risk of an incident gout attack per 10 g increase in daily alcohol intake is 1.17 (95% CI, 1.11–1.22), but this increases to 1.49 (95% CI, 1.32–1.70) per daily serving of beer. Wine consumption was not previously associated with an increased relative risk for incident gout attacks [59], but a prospective Internet-based case-crossover study demonstrated an increased risk of recurrent gout attacks from even moderate alcohol consumption of all types, including wine [61]. Compared with no alcohol intake, consuming >1-2 servings of wine over the prior 24 hours increased the risk of recurrent gout attack by an odds ratio of 2.38 (95% CI, 1.57-3.62). Among all alcohol types, the risk of flare was 1.36 times higher for >1-2 alcoholic beverages (95% confidence interval [CI], 1.00-1.88) and 1.51 times higher for >2-4 beverages (95% CI, 1.09-2.09).

Other recommended lifestyle changes include maintaining hydration levels with water intake >2 L/day, and alkalization of the urine using potassium citrate to mitigate the risk of recurrent kidney stone formation. Additionally, Vitamin C supplementation may be of value in the prevention or management of gouty arthritis. In a placebo-controlled, double-blind randomised study, vitamin C supplementation (500 mg/day for 2 months) in non-smoking healthy volunteers was shown to significantly reduce serum urate levels (mean change, -0.5 mg/dL; 95% CI, -0.6 to -0.3), whereas patients receiving placebo had a slight increase in serum urate levels [62]. Finally, in patients with gouty arthritis, it is important to recognize potential comorbidities and associated concomitant medications that could increase SUA levels, including thiazide or loop

diuretics, low-dose aspirin, cyclosporine, niacin, pyrazinamide and ethambutol [63].

Pharmacologic management

Maintenance of serum urate concentrations below the saturation point for MSU (≤ 360 µmol/L or ≤ 6mg/dL) promotes crystal dissolution and prevention of MSU crystallization [24], and the target serum MSU concentration is lower in severe gout (≤ 300 µmol/L) [30]. Initiation of urate-lowering therapy is traditionally started 2 weeks after, not during, an acute attack [24,64]. However, initiation of allopurinol 300 mg/day did not increase flare frequency compared to placebo in a study of 51 patients with acute gout [65]. The 2012 ACR guidelines state that initiation of urate-lowering therapy (ULT) can be done during an acute attack after anti-inflammatory pharmacotherapy is started [27]. However, the 2016 ACP guidelines recommend against ULT in patients with single or infrequent flares, given a lack of long-term studies on ULT in these patients [29]. Citing studies showing ULT did not decrease gout flare frequency in the first 6 months, they concluded the evidence was insufficient regarding the benefits of treating to a target SUA against the harms of SUA monitoring and medication escalation. Regarding ULT in patients with recurrent attacks, it was recommended to first discuss with the patient the benefits, harms, costs, individual preferences and prophylaxis. Meanwhile, 2016 EULAR guidelines state that ULT should be discussed with the patient from the first presentation of gout, with early initiation recommended in those <40 years old, with SUA>8 mg/dL, and/or comorbidities e.g. renal or cardiac disease [24]. Treatment is clearly indicated in all patients with severe established gouty arthritis, and may also be considered in less severe disease to decrease the crystal load. Since introduction of urate-lowering therapy is associated with an initial increase in acute gout flares, concurrent prophylaxis with colchicine or NSAIDs is recommended for up to 6 months [24,27]. In patients for whom both are contraindicated and/or ineffective, then low dose prednisone or prednisolone up to 10 mg/day can be considered [27]. Duration of treatment is typically lifelong, especially in those with SUA>8.5 mg/dL. But this may not be necessary in motivated patients with SUA ≤ 7.5 mg/dL, who can decrease it by 1-2 mg/dL with lifestyle changes such as becoming a strict vegetarian and losing weight, e.g. via bariatric surgery (Figure 4).

Allopurinol

The mainstay of long-term urate-lowering therapy is allopurinol, which has been used in the treatment of gout for several decades [24]. A xanthine oxidase inhibitor (XOI), it blocks the production of uric acid by reducing purine catabolism [66]. Typical adverse events include rash, diarrhoea, nausea and increases in alkaline phosphatase, ALT and AST levels. Clinical trials have demonstrated the efficacy of allopurinol against placebo, while head-to-head trials against other approved medications include febuxostat (described below) and benzbromarone [67,68]. Against the latter, there was no difference in efficacy after dose escalation of both [68].

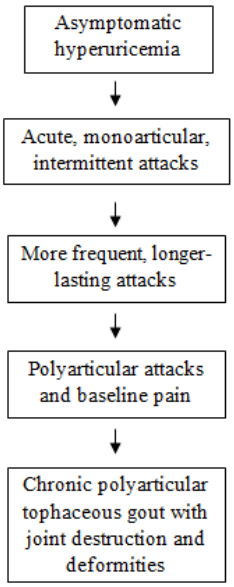

Figure 4: Natural Progression of Gout.

In patients with normal kidney function, the recommended starting dose is 100 mg/day, which should be titrated upward to achieve target SUA <6 mg/dL; this was achieved in 78% patients in one study at a dose of 600 mg/day [24,68]. The long-term safety of higher doses of allopurinol has not been established, and caution is advised in patients with renal impairment, mainly due to the increased risk of serious cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms, and toxic epidermal necrolysis [69,70]. Therefore, allopurinol should be stopped at the first sign of an allergic reaction such as a skin rash [66]. The risk of severe hypersensitivity reaction to allopurinol is particularly increased in patients with chronic renal insufficiency who are also positive for a certain HLA genotype, HLA-B58 [71]. Therefore, polymerase chain reaction screening for this allele should be considered in the Korean (with CKD Stage 3), Han Chinese, and Thai ethnic groups prior to initiation of allopurinol [27].

Probenecid

A uricosuric agent, probenecid blocks tubular reabsorption, which allows increased excretion of uric acid [64]. It has moderate urate-lowering effect as monotherapy or combination therapy with allopurinol when the target SUA is not achieved with the latter alone [72]. It should be administered at 250 mg twice daily for 1 week and then 500 mg twice daily thereafter. In patients whose symptoms remain uncontrolled or where 24-hour uric acid excretion is less than 700 mg, the dose can be titrated up by 500 mg/day increases every 4 weeks, unless toxicity occurs [64]. Typical adverse events include headache, dizziness, hepatic necrosis, vomiting and nausea. In addition, an alkali urinary pH should be maintained using either sodium bicarbonate (3-7.5 g/day) or potassium citrate (7.5 g/day), together with liberal fluid intake. Contraindications to

probenecid include known blood dyscrasias or uric acid kidney stones.

Febuxostat

Another agent approved for the chronic management of hyperuricemia in patients with gouty arthritis is febuxostat, a non-purine XOI which therefore restricts the synthesis of uric acid from hypoxanthine and xanthine [73]. 2012 ACR guidelines include it as first-line treatment to control SUA [27,28], whereas 2016 EULAR gudelines reserve its use for when target SUA cannot be achieved with allopurinol, due to its cost [24]. Although both are XOIs, animal studies showed a more potent and longer lasting hypouricemic effect from febuxostat compared to allopurinol, an effect attributed to its potent inhibition of both oxidized and reduced forms of xanthine oxidase [74]. The approval of febuxostat was based on the data from 3 phase III clinical trials, APEX (Allopurinol- and Placebo-Controlled Efficacy Study of Febuxostat) [75]; FACT (Febuxostat Versus Allopurinol Controlled Trial) [76]; and CONFIRMS (A Phase 3, Randomized, Multicenter, Double-Blind, Allopurinol-Controlled Study Assessing the Efficacy and Safety of Oral Febuxostat in Subjects With Gout) [77]. In all of these studies, patients receiving febuxostat (80-240 mg/dL) had a significantly higher SUA response rate (the primary endpoint) compared with allopurinol (200-300 mg/dL) [75-77]. However, allopurinol was limited to no more than 300 mg/dL in these studies, although higher doses are frequently required for patients with moderately severe tophaceous gout [66]. In APEX and FACT, naproxen (250 mg twice daily) or colchicine (0.6 mg/dL) was administered as flare prophylaxis for 8 weeks, and the incidence of gout flares was highest during the 4 weeks immediately after withdrawal of prophylaxis [77]. But when flare prophylaxis was administered for the full 6-month treatment period in the CONFIRMS trial, there was actually a steady decline in the incidence of flares throughout those 6 months with no increased risk of adverse effects [78]. These studies showed generally comparable adverse events across all treatment groups, most commonly liver function abnormalities, diarrhoea, rash, arthralgia and headache [73,75-77].

Benzbromarone

Like probenecid, benzbromarone is a uricosuric but exerts a stronger effect [79]. As with probenecid and febuxostat, it is indicated when allopurinol fails to reach target SUA [24], based on a study demonstrating successful treatment in 92% patients on benzbromarone after allopurinol 300 mg/day failed to achieve SUA goals; the probenecid success rate was significantly lower at 65% with P=0.03 compared to benzbromarone [79]. Additionally, it was better tolerated than allopurinol [79] but is still contraindicated at eGFR <30 mL/min [24]. A dose escalation trial for benzbromarone and allopurinol showed equivalent efficacy at higher doses of both (benzbromarone 200 mg/day and allopurinol 600 mg/day) [68].

Treatment of Chronic, Refractory or Tophaceous Gouty Arthritis

Pegloticase

Humans lack a functional gene of enzyme urate oxidase, but in most mammals, it catalyzes the conversion of uric acid to 5-hydroxy isourate and hydrogen peroxide, ultimately leading to the formation of allantoin, which is a more soluble and easily excreted purine metabolite [80,81]. A genetically engineered pegylated mammalian urate oxidase enzyme, pegloticase is indicated for treatment of chronic gout refractory to conventional therapy, including failure to achieve target SUA or when symptoms are inadequately controlled with combinations of XOI and uricosurics at maximum tolerated doses [24,82]. However, a primary concern is that the formation of antibodies to the drug limits its efficacy and tolerability. In phase III clinical studies, more than 25% of treated patients developed infusion-related reactions, despite pretreatment with fexofenadine, acetaminophen and hydrocortisone [83]. The GOUT1 and GOUT2 phase III clinical trials demonstrated that pegloticase (8 mg biweekly or monthly) resulted in lower uric acid levels compared to placebo [84]. Pooling the data from both trials, serum uric acid <6.0 mg/dL was achieved in 42% patients in the biweekly group (36/85; 95% CI, 32%-54%, P<.001), 35% patients in the monthly group (29/84; 95% CI, 24%-46%, P<.001), and 0% patients in the placebo group (0/43; 95% CI, 0%-8%; P<.001). Furthermore, complete tophus resolution (defined as complete resolution of ≥ 1 tophus without increase in size of any other tophus or appearance of new tophus) was significantly higher in patients receiving biweekly pegloticase compared with those receiving placebo by 6 months (45% *vs.* 8%, P=.002) [85]. Gout flares were more frequent in both pegloticase groups for the first three months, with the mean flare frequency 2.3 for biweekly (P=0.01) and 2.7 for monthly (P<0.01) compared to 1.3 for placebo, but were significantly less in the biweekly group compared to placebo during the next three months (0.8 *vs.* 1.3, P=0.06) [84]. Of the infusion-related reactions occurring in 45% patients receiving pegloticase (94/208), 91% occurred when preinfusion serum uric acid was >6.0 mg/dL, reflecting loss of urate-lowering efficacy. Therefore, discontinuation of pegloticase upon preinfusion serum uric acid >6.0 mg/dL will likely decrease the incidence of infusion reactions [86].

Lesinurad

A novel uricosuric, lesinurad is a selective uric acid reabsorption inhibitor which inhibits urate transporter 1 (URAT1) and organic anion transporter 4 (OAT4). In replicate randomized, placebo-controlled, phase III trials (CLEAR1 and CLEAR2), lesinurad was added to patients in whom SUA targets were not achieved with allopurinol alone [87,88]. At 6 months, combination therapy with lesinurad 200 mg+allopurinol and lesinurad 400 mg+allopurinol improved the proportion of patients meeting target SUA <6 mg/dL compared to allopurinol +placebo (54.2%, 59.2%, and 27.9%, respectively, P<0.0001, in CLEAR1; and 55.4%, 66.5%, and 23.3%, respectively, p<0.0001, in CLEAR2). However, key secondary endpoints of gout flares and

tophus resolution were not improved. Treatment-emergent adverse events (TEAE) were more frequent in the lesinurad 400 mg group but mostly Grade 1 or 2. Serum creatinine elevation was increased in the lesinurad groups, especially at the 400mg dose, but this generally resolved without cessation of lesinurad and was postulated to have been from increased uric acid microcrystallization in the renal tubules. The overall adverse effect profile of lesinurad 200 mg was comparable to allopurinol alone.

Other novel pharmacologic agents under investigation for gout include topiroxostat, arhalofenate, ulodesine, and levotofisopam. Topiroxostat is a potent, hybrid-type inhibitor of xanthine oxidoreductase that binds both competitively to the channel and to molybdenum in the hydroxylation reaction intermediate. Early trials have shown promise for the treatment of hyperuricemia and chronic kidney disease [89,90]. A phase III trial showed topiroxostat 120 mg/day was non-inferior to allopurinol in lowering uncontrolled SUA in patients with gout or asymptomatic hyperuricemia; additionally, adverse events were comparable in both groups [90]. Originally studied for use in diabetes, arhalofenate is an anti-inflammatory uricosuric agent that targets the tubular transporter URAT1 and inhibits the urate crystal-induced production of IL-1β. A phase II trial showed combination therapy with febuxostat significantly decreased SUA compared to either alone, and was well-tolerated [91]. An inhibitor of purine nucleoside phosphorylase (PNP), ulodesine interferes with the formation of new uric acid upstream of xanthine oxidase. In a phase IIb study in patients with hyperuricemia despite allopurinol, patients receiving ulodesine met the target serum uric acid more frequently, although there was a dose-related decrease in CD4 count resulting in protocol-specified withdrawals. A novel uricosuric agent, levotofisopam is the S-enantiomer of racemic tofisopam, a benzodiazepine derivative. Early studies on its use as monotherapy have shown a reduction in serum uric acid and a favorable safety profile [92,93].

Summary

Gouty arthritis is the most common inflammatory arthritis in males over the age of 40 years, but it is also one of the most misunderstood diseases. Hyperuricemia is a requirement to develop gouty arthritis. Upon oversaturation of serum urate, typically above 6.8 mg/dl, MSU can crystallize in tissue including the joint, giving rise to gouty arthritis. Phagocytosis of coated MSU crystals by macrophages leads to activation of the 'inflammasome', a cytosolic multiprotein complex. This in turn activates of a series of pro-inflammatory enzymes such as caspases promoting the maturation of IL-1 ß, a pro-inflammatory cytokine, culminating in neutrophil influx into the synovium that characterizes the highly inflammatory nature of acute gouty arthritis. Management of this condition involves treatment of the acute attack, addressing the underlying metabolic abnormality of the hyperuricemia, and providing prophylaxis to the patient to prevent recurrence until normouricemia is achieved. Here, serum urate lowering is usually accomplished by the use of xanthine oxidase inhibitors such as allopurinol or febuxostat, or intravenous pegloticase (uricase). Treatment of acute gout flares has historically included NSAIDS, colchicine, and corticosteroids, but a substantial proportion of especially elderly patients are either unresponsive to or intolerant of the use of these medications because of the significant co-morbidities such as renal failure, cardiovascular disease or being at risk for gastrointestinal bleeding. In these patients, the advent of IL-1 blockade represents a promising new treatment modality to treat acute gouty arthritis and prevent frequent painful flare-ups.

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