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Current Management Concepts in Gouty Arthritis

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Abstract:

Background- Gouty arthritis is an extremely painful condition that causes functional impairment. Longstanding elevation of the serum uric acid level can lead to the deposition of monosodium urate crystals, causing gout (arthritis, urate nephropathy, tophi). Gouty arthritis has become increasingly complex because of multiple comorbidities, iatrogenic factors and hyperuricemia that is refractory to treatment. In this review, we present a general overview of gouty arthritis including its pathophysiology, clinical presentations, diagnosis, management and emerging therapies to treat gouty arthritis and flares.

Materials and Methods: Selective literature review on the diagnosis and treatment of gout.

Results & Conclusion: Asymptomatic hyperuricemia is generally not an indication for pharmacological intervention to lower the uric acid level. When gout is clinically manifest, however, acute treatment of gouty arthritis should be followed by determination of the cause of hyperuricemia, and long-term treatment to lower the uric acid level is usually necessary. The goal of treatment is to diminish the body's stores of uric acid crystal deposits and thereby to prevent the inflammatory processes that they cause, which lead to structural alterations. The available medications for this purpose are allopurinol and various uricosuric agents, e.g., benzbromarone. There is good evidence to support the treatment of gouty attacks by the timely, short-term use of non-steroidal anti-inflammatory drugs , colchicine, and glucocorticosteroids. Additional newer drugs such as IL-1 inhibitors have been developed to improve the management of resistant gout.

Key words: *Gout, Hyperuricemia, Diagnosis, Treatment*

Introduction

Gout can be defined as a disorder of purine metabolism of varied etiology, characterized by hyperuricemia and precipitation and deposition of inflammatory monosodium urate (MSU) crystals in synovial and other tissues, accompanied by extreme pain. The prevalence of gout has increased in recent years and currently affects 1.4% of the adult population, making it the most common form of inflammatory arthritis in men and in older women. Compared with women, men have a four- to nine-fold increased risk of developing gout. Women often do not develop gout until they reach menopause, when the uricosuric action of estrogens is lost. Because of changing dietary and other lifestyle habits, at least 1% to 2% of all adults in the industrialized nations are now affected by gout.

The following issues are both crucial and challenging in management of gouty arthritis: (i) modification of lifestyle; (ii) use of urate-lowering therapy (ULT) to minimize gouty arthritis flares; (iii) use of alternative drugs for patients who are unresponsive or have adverse reactions to traditional drugs such as colchicine and nonsteroidal anti-inflammatory drugs(NSAIDs); and (iv) surgical management for gout-related complications. Recently, an improved understanding of the pathophysiology of gouty arthritis, including the identification of many genetic factors, has contributed to facilitating new therapeutic modalities. New innovative drugs such as anti-interleukin inhibitors and non-xanthine oxidase inhibitors have been developed for treating gouty arthritis. Guidelines that have been developed by the European League Against Rheumatology (EULAR) and the British Society for Rheumatology are available for both specialists and non-specialists. Each of these was produced by a professional rheumatological body and was based on a comprehensive analysis of the evidence base as represented by the current international literature. With the development of new treatment modalities, these pragmatic guidelines require updating to include current best management.

This review article aims to shed light on the subject of the diagnosis and treatment of gout and present guidelines for medical practice

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Patho-physiology

Urate is the end product of purine metabolism. Important steps in this are the degradation of xanthine and hypoxanthine by the enzyme xanthine oxidase. Urate is excreted primarily via the kidneys.

Genome-wide association studies for serum urate have identified 28 loci influencing serum urate levels commonly SLC2A9, ABCG2, PDZK1, SLC22A12, PRPSAP1 and Glycolytic genes), genes encoding transporters that excrete uric acid in the kidney and gut. Polymorphisms in the corresponding genes lead to a disturbance in the function of the transporters, with reduced renal urate excretion and consequent accumulation of urate, and are often associated with gout .

In accordance with physicochemical laws, once uric acid has passed its saturation point of 400 μmol/L (6.8 mg/dL; at 37 °C, pH 7.4), it starts to precipitate out in the form of monosodium urate crystals. Sites of predilection are peripheral regions of the body (e.g., the joints of the extremities) when ambient temperatures are low and inflamed joints. Urate crystals lead to activation of the NALP3 inflammasome with release of proinflammatory cytokines, among them interleukins 1, 18, and 8, and of tumor necrosis factor, attracting more polymorphonuclear neutrophilic granulocytes.

In gouty arthritis, bone destruction seems to result from an imbalance in bone remodeling. Lee and colleagues proposed that bone destruction in chronic gouty arthritis is at least in part

dependent on expression by T cells of receptor activator of NF-κB ligand (RANKL) . Overexpression of RANKL promotes osteoclastogenesis, which is characterized by T cell infiltrates in a proinflammatory environment. Concomitantly, the RANKL antagonist osteoprotegerin is downregulated. Tophus-associated monocytes contribute tumor necrosis factor-α, IL-1β and IL-6, which play roles as additional promoters of osteoclast differentiation. Recent research has shown that factors such as IL-1β play important roles in this pathway .

Clinical Features

The manifestations of gouty arthritis range from asymptomatic hyperuricemia to advanced tophaceous gouty arthritis. Despite the fact that hyperuricemia substantially increases the risk of gouty arthritis flares, it is still relatively difficult to predict who will develop them. It must be emphasized that not all individuals with hyperuricemia develop gouty arthritis.

Although clinical symptoms include swelling, redness and warmth, acute gouty arthritis is typically characterized by rapid onset of pain in the affected joint. Gouty arthritis commonly involves extremity joints such as the first metatarsophalangeal joint (podagra), ankle, knee, wrist and elbow; typically is very painful, starts at night, lasts around a week, and in many cases is self-limiting. Almost 90% of patients who have suffered an attack of gout experience repeat episodes during the following 5 years. Chronic gouty arthritis is characterized by intense inflammation, persistent joint abnormalities, tophi and nephrolithiasis. However, Konatalapalli et al. reported that axial gout may be a common feature of chronic gouty arthritis. Clinicians should be aware of spinal involvement with associated back pain in patients with gouty arthritis.

Diagnosis

It is quite common for the serum urate level to be normal or low during an attack, so the best time to measure it is 2 to 3 weeks after an attack. If the manifestation is atypical and serum urate normal, joint puncture should be done to demonstrate the presence of crystals under a polarization microscope. The crystals appear as birefringent intra- and extracellular needles 10 to 20 μm in length. The presence of intracellular MSU crystals in synovial fluid or in aspirates from tophi is diagnostic of gouty arthritis. If infection is suspected, aspiration is recommended .

In younger patients with a family history of gout, then owing to the frequent association with impaired renal function, serum creatinine should be determined, 12- or 24-hour urinary clearance of creatinine and urate, and a urinary pH strip test should be performed .

Conventional radiography, ultrasound, CT, and MRI contribute to the diagnosis and assessment of gouty arthritis . The radiologic features in soft tissue, bone and joints of patients with chronic tophaceous gout are not usually seen until 6–12 years after the initial attack. The soft tissue findings consist of calcific deposits and eccentric juxta-articular lobulated masses (hand, elbow, knee, ankle and foot). Bone findings include “mouse bites” from erosion of long-standing soft-tissue tophi, bone infarction, “punch-out” lytic bone lesions and sclerosis of margins. Joint findings comprise erosion of joint margins with sclerosis, cartilage destruction and periarticular swelling.

CT has potential both as a diagnostic tool in gout and as an instrument with which measure progressive erosive damage and, indeed, tophus growth and resolution.

DECT (Dual-energy CT), a recent arrival on imaging studies has been shown to help diagnose gout in those patients for whom joint aspiration is not possible. It has a potential to quantify urate using automated, computerised volume assessment software, providing reproducible data that may be stored digitally and compared with subsequent measurements over time to follow the reduction in urate burden achieved with effective ULT. It also enables measurement of the crystal component of tophi, however further studies are warranted.

ULTRASONOGRAPHY (USG) has an emerging role in gout, to both facilitate joint aspiration for confirmation of the presence of MSU crystals and measurement of tophi (if at accessible site) to monitor the efficacy of ULT. Typical features of tophi on USG include ovoid shape, hypoechoic border, stippled center, and lack of vascularity. The double-contour sign described by Thiele and Schlesinger on USG is yet to be recommended as a reliable diagnostic feature.

Ito et al. reported that 18 F-fluorodeoxyglucose positron emission tomography demonstrated focal uptake in multiple joints, including the bases of both big toes, and in dense masses in the juxta-articular soft tissue of the elbows in a patient with gouty arthritis with tophi.

Management Of Gouty Arthritis

The protocol for management of gouty arthritis focuses on the following objectives:

(i) alleviating the pain and inflammation that accompanies acute gouty arthritis flares; (ii) preventing recurrence of gouty arthritis flares; and (iii) preventing urate crystal deposition by prescribing long-term ULT.

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Lifestyle Modification

Historically, gout was termed the "disease of kings" because it was associated with eating rich foods and consuming excessive alcoholic beverages. Modifications of lifestyle and diet are key components of gout management although they alone have a small urate-lowering effect. However, Su et al. have pointed out that, regardless of the many other relevant environmental and nutritional factors, gout involves homeostatic imbalance of essential trace elements caused by genetic factors and has a unique expression profile of these elements. Much epidemiological research has demonstrated alcohol drinks are independent risk factors for gout. Fructose , meat, seafood, sugar-sweetened soft drinks increase the risk of developing gout, whereas dairy products, coffee, and vitamin C seems to be protective against development of gout. A recent randomized controlled trial (RCT) has found that intact milk has an acute uricosuric urate lowering effect because it contains proteins in the form of casein, lactalbumin and orotic acid.

Treatment Of Acute Gout

Acute attacks of gout should be treated resting the affected joint and treating them with ice, which has significant additional anti-inflammatory effect. The American College of Rheumatology (ACR) guidelines for the treatment of acute gout recommended initiating drug therapy within 24 hours of the onset of the acute attack (based on the consensus that
early treatment leads to better outcome). It is proposed that during the acute attack, ULT be continued without interruption. Pharmacological treatments, including NSAIDs and colchicine, are the most frequently used.

NSAIDs are commonly used in patients who do not have underlying comorbidities. The most important determinant of therapeutic success is how soon the NSAID is initiated, and that large enough dosages be given at the onset of symptoms and continued over a long period of time. In 2 studies comparing etoricoxib with indomethacin, etoricoxib 120 mg once daily was comparable with indomethacin 50 mg 3 times daily in treating acute gout. Studies comparing celecoxib (400 mg and 800 mg) and indomethacin 50 mg 3 times daily show equivalence between celecoxib and indomethacin. If the patient has a history of gastrointestinal ulcers or bleeding, proton pump inhibitors should be given in addition. However, the British Society for rheumatology and EULAR recommend NSAIDs as an option for prophylaxis of gouty arthritis flares. In addition, Zhou et al. reported that acupuncture combined with infrared irradiation is more effective than oral indomethacin for acute gouty arthritis as it provides significant analgesia without impairing liver function.

Colchicine, which blocks microtubule assembly and reduces transport of MSU crystals, is the standard medication for preventing flares during initiation of ULT. The US Food and Drug Administration approved colchicine for prophylaxis of gouty arthritis flares in 2009. Borstad and colleagues performed a randomized, double-blind, study on colchicines and experienced fewer flares over 6 months. However, the incidence of diarrhea was higher with colchicine group. Alternatively, so long as renal function is normal, colchicine may be given; at a dosage of 0.5 mg every 2 hours, this settles the gout attack
within 1 day for 80% of patients. However, high doses often lead to nausea and diarrhea but given up to three times at a dose of 0.5 mg/d, it is usually well tolerated and adequately effective. When administering colchicine with inhibitors of CYP3A4 or P-glycoprotein, dosage adjustment is also necessary because of the increased risk of colchicine-induced toxic effects.

Corticosteroids are commonly used in patients who cannot be treated with NSAIDs and/or colchicines. The American College of Rheumatology (ACR) Task Force Panel (TFP) recommended prednisolone at a dose of 0.5 mg/kg/d for 5 to 10 days, or for 2 to 5 days at this full dose followed by a 7to 10 day taper. Once symptoms are controlled, maintenance therapy is based on minimum doses and the shortest possible duration to avoid side-effects. Intra-articular corticosteroid are beneficial and useful in acute gout when 1 or 2 joints are inflamed ensuring that the joint is not infected.

Adrenocorticotropic hormone (ACTH) may inhibit gouty inflammation peripherally by activating the melanocortin type 3 receptor (MC3R) though exact mechanism of action is not well understood. A retrospective study of 33 patients who received ACTH for their acute gout or pseudogout attacks found that 40 IU administered intramuscularly every 8 hours for 1 to 14 days; a 97% resolution rate with the mean time to complete resolution was 5.5 days, and a relapse rate of 11%.

Current Interleukin-1β inhibitors in trials include anakinra, canakinumab, and rilonacept has now been shown to have a beneficial effect in gouty inflammation. Canakinumab is approved by the European Medicines Agency (EMEA) for the treatment of adult patients with frequent gout attacks in whom NSAIDs and colchicines are contraindicated, are not tolerated, or do not provide an adequate response, and in whom repeated courses of

corticosteroids are not appropriate. It is important to note that, although rilonacept and canakinumab both inhibit the IL-1β pathway, rilonacept also binds IL-1α whereas canakinumab binds selectively to IL-1β.

Long Term Management Of Gout

Urate –Lowering Therapy (ULT): It is now generally accepted that persistent chronic inflammation is often present in patients with gouty arthritis, even when the patient is asymptomatic. Rapid changes in serum uric acid (SU) concentrations during the initial stages of ULT are associated with an increased risk of acute gouty arthritis flares. Becker and colleagues proposed that the increased flare rate that occurs when SU concentrations change rapidly because of ULT might be attributable to alterations in the physical or chemical state of pre-existing MSU crystals. According to this theory, when SU concentrations decrease the relative balance of remodeling and mechanical disruption alters the stability of tophi in the affected joint. Superficial MSU crystals dissolve, which exposes uncoated MSU crystals to synoviocytes and monocytes, stimulating expression of proinflammatory cytokines including IL-1 and IL-8.

Pharmacological ULT has traditionally been initiated in the interval between attacks because of concern that immediate urate reduction might worsen or prolong an ongoing attack. Although a recent small trial found no significant difference in symptoms or levels of inflammatory markers between patients started on allopurinol during an attack and those beginning treatment 2 weeks later. Neogi recommend the traditional approach, with only rare exception.

Serum Urate Goals and Monitoring:The most widely recommended serum urate goal-range during ULT is less than 6 mg/dl. A goal serum urate of less than 5 mg/dl is recommended for patients with tophi because these lesions signify more advanced gout, and lower serum urate levels are associated with more rapid tophus resolution. Recommendations for measurement of serum urate concentration 2 to 4 weeks after each dose adjustment and twice within the first 6 months after goal range is achieved.

Perez-Ruiz and colleagues have suggested that once gout symptoms and signs have resolved for several years, the goal of ULT may be reset at a higher level in the subsaturating range, allowing lower dose maintenance ULT.

Urate Lowering Pharmacological Strategies

1)Reduction of uric acid production via xanthine oxidase inhibitors:

a) Allopurinol and its major active metabolite, oxypurinol both competitively inhibit xanthine oxidase activity and decreases rate of urate production, though less specific than febuxostat. Allopurinol should be gradually titrated up with the serum urate level being monitored. Treatment starts with 100 mg and depending on the urate value is increased by 50 to 100 mg per week until a maximum of 800 mg is reached. In a patient with reduced kidney function, the dosage must be matched to the glomerular filtration rate (GFR < 30 mL/min: 100 mg allopurinol every second day).

Most allopurinol-related skin rashes are mild, but skin rash can herald development of an allopurinol hypersensitivity reaction, including toxic epidermal necrolysis, Stevens-Johnson syndrome, and AHS (Allopurinol hypersensitivity syndrome) consisting of an erythematous rash, fever, hepatitis, eosinophilia, and acute renal failure. Risk factors for allopurinol hypersensitivity reactions include female gender, age, chronic kidney disease, diuretic therapy, recent initiation of allopurinol, and HLA-B*5801 halotype. Although successful desensitization to allopurinol has been reported in patients with milder reactions, Neogi do not recommend densensitization in patients with prvious features of serious allopurinol hypersensitivity.

b) Febuxostat selectively inhibits both oxidized and reduced forms of xanthine oxidoreductase by noncompetitive mechanisms, thereby reducing serum urate levels and urinary uric acid excretion. Metabolism of febuxostat is mainly hepatic so it can be used in patients with renal failure. It has fewer drug-drug interactions and lastly in patients who have had (or are at high risk for) an allopurinol hypersensitivity reaction.

Randomized clinical trials have confirmed urate lowering efficacy and safety for febuxostat at once-daily doses ranging from 40 mg to 120 mg. Although 2012

American College of Rheumatology guidelines recommend either allopurinol and febuxostat as first line ULT agents.

2) Uricosuric agents: Probenecid, Benzbromarone, and Sulfinpyrazone

These are weak organic acids that promote uric acid clearance by inhibiting proximal tubule urate anion transporters that mediate urate reabsorption. These agents has been used sparingly because they are not first-line agents for patients with uric acid overproduction or high risk of urolithiasis, multiple daily dosing and drug-drug interactions are especially seen with probenecid.

Benzbromarone is highly effective, single-daily-dose agent including population having a substantial frequency of the HLA-B*5801 risk halotype for severe allopurinol adverse reactions.

Adjunctive agents with uricosuric properties like Losartan and Fenofibrate can be useful in patients of gout with hypertension or hyperlipidemia. Vitamin C may also have a mild but persistent urate-lowering effect at doses as low as 500 mg daily.

Recombinant Uricase Therapy:

Pegloticase is a modified porcine recombinant uricase which converts uric acid to allantoin. Repeated infusions (8 mg IV infusions biweekly) promote resorption of urate crystal deposits in tissues and reduce the body urate pool, with subsidence of the crystal-induced inflammatory and destructive processes mediating the clinical events of gout. There was high frequency of adverse events, most commonly gout flares and immune reactions. It should be considered for the patients with gout refractory to or intolerant of oral ULTs.

Emerging Therapies

Lesinurad is a uricosuric agent, major metabolite of nonnucleoside reverse transcriptase inhibitor, RDEA809 inhibits both URAT-1 and OAT4 transporters in the renal tubule. Two phase 2b trials of lesinurad on gout patients with renal impairment were conducted and demonstrated increased renal excretion of uric acid at 200, 400, and 600 mg daily doses, with no attributable serious adverse events.

Another multicenter open-label trial investigated the efficacy and safety of lesinurad in combination with febuxostat and demonstrated that combining drugs with complementary mechanisms of action produced significantly greater reductions in serum uric acid than increasing the dose of a single agent.

Ulodesine is an oral once-daily purine nucleoside phosphorylase inhibitor that blocks production of uric acid. A phase 2 trial tested the urate lowering effects of combining low-dose ulodesine (20, 40, and 80 mg/d) with various doses of allopurinol and observed synergistic reduction in serum urate achieving the target serum uric acid of less than 6.0 mg/dl.

Levotofisopam is the s-enantiomer of racemic tofisopam, a 2,3-benzodiazepine derivative showed urate-lowering capacity with acceptable safety and tolerability. An open-label phase

2a trial was carried out in 13 gouty subjects, and target urate level of less than 6.0 mg/dl was achieved in all the subjects.

Arhalofenate was noted to have uricosuric properties in test subjects, shown to inhibit the uric acid transporters URAT-1, OAT4, and OAT10. Four phase 2 trials of 3 to 6 months duration have been carried out and substantial uricosuria was demonstrated with decrease in serum urate ranging from 20% to 40%.

Anti-inflammatory Therapy In Gout

Based on both experimental and clinical observations, IL-1β is the cytokine that is located at the start of the inflammatory cascade in gout. The NLRP3-inflammasome is essential for the production of IL-1β when macrophages are incubated with monosodium urate crystals.

Anakinra is an IL-1 inhibitor with a half life of 4 to 6 hours. In a larger case series, more than 60% of patients reported a very satisfactory and rapid resolution of symptoms of acute gout. The overall impression is that it is able to control acute attacks that are refractory to corticosteroids.

Canakinumab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody specific for IL-1β with a half life of around 28 days. Two publish studies (phase 2 and 3) concluded that a single dose of canakinumab (150 mg) was effective in relieving pain and symptoms of acute gout, and was superior to triamcinolone in terms of its rapid onset of action and reduction of subsequent gout flares.

Rilonacept (or IL-1 Trap)is a fusion protein formed by the ligand-binding domain of the extracellular part of IL-1R1 and IL-1 receptor accessory protein (IL-1RAcP) linked to the Fc portion of human IgG1 with half-life of 9 days has been approved for the use in the treatment of acute gout in Europe. It was initially reported to be effective for chronic gouty arthritis in ; in a subsequent study of acute gout, when rilonacept was compared with indomethacin or the combination of both, it was not shown to be superior to the comparator.

Caspase Inhibitors:

Caspases (caspase-1 and -5) are necessary for the intracellular processing of pro-IL-1β secretion, and its inhibition will block IL-1β secretion. However there are only scant reports documenting their clinical efficacy

in humans, even though these inhibitors were effective in animal models of inflammation. One potential problem might be cross-reactivity with other caspases.

Clinical Relevance:

The significance of this article is to have a thorough understanding of pathology, diagnosis and various treatment modalities essential for optimal individualization of management regimens. The goal of treatment is to diminish the body's stores of uric acid crystal deposits and thereby to prevent the inflammatory processes that they cause, which lead to structural alterations.

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