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Treatment of hyperuricaemia and gout

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Introduction

Gout is the most prevalent inflammatory arthritis, affecting 1.4% of adults in the UK.[1] Chronic elevation of serum uric acid (SUA), or hyperuricaemia, is required for gout to develop. Risk factors for hyperuricaemia and gout are summarised in Box 1. When the SUA level increases above the physiological saturation threshold, monosodium urate (MSU) crystals precipitate in and around peripheral joints. After a prolonged period of asymptomatic hyperuricaemia, gout typically presents clinically as an acute attack of excruciating joint pain, swelling and tenderness, commonly affecting the first metatarsophalangeal joint. Attacks characteristically resolve over 2–3 weeks, but most patients subsequently experience recurrent attacks involving other joints and can develop joint damage and clinically apparent subcutaneous MSU crystal concretions (tophi) (Fig 1). Treatment aims to first relieve the severe pain and inflammation of acute gout and then to reduce the SUA level sufficiently to prevent crystal formation and to dissolve existing crystals, thereby preventing further attacks and irreversible joint damage.

Box 1. Risk factors for hyperuricaemia and gout.[1]

- Male gender
- Family history and/or genetic factors
- Metabolic syndrome
- Hypertension
- Insulin resistance
- Obesity
- Dietary factors (increased risk)
  - alcohol (particularly beer)
  - purine-rich foods (red meat and seafood)
  - fructose and sugar-sweetened soft drinks
- Dietary factors (reduced risk)
  - cherries
  - vitamin C
  - dairy products
  - coffee
- Medication
  - diuretics (loops and thiazides)
  - ciclosporin
  - pyrazinamide
  - ethambutol
- Impaired renal function
- Osteoarthritis (gout only)
- Chronic lead poisoning
- Myeloproliferative disorders

Management of acute gout

Treatment of acute gout aims to provide rapid relief of pain and inflammation. The affected joint should be rested and the application of local ice-packs can safely reduce pain and swelling.[2] Pharmacological options are oral non-steroidal anti-inflammatory drugs (NSAIDs), oral colchicine and corticosteroids.[3,4] Although no individual NSAID appears superior to another, any quick-acting NSAID can be used at the full dose together with a proton pump inhibitor. Indometacin is best avoided in view of frequent gastrointestinal, central nervous system and cardiovascular adverse effects. Until recently, oral colchicine was often used in high doses, which frequently led to severe diarrhoea, nausea or vomiting.[5] However, current advice is to use a lower dose of 500 µg two to four times daily, which remains effective and is better tolerated.[3,4,6,7]

The single most effective treatment for acute gout is combined joint aspiration (immediately reducing intra-articular pressure and severe pain) and injection of intra-articular corticosteroid. This is particularly appropriate when NSAIDs and colchicine are contra-indicated or poorly tolerated and enables a definitive diagnosis by synovial fluid MSU crystal identification. Intramuscular or oral corticosteroids (eg prednisolone 20 mg daily) are effective alternatives when NSAIDs and colchicine are not appropriate, when attacks are oligo- and/or polyarticular or when monoarticular attacks occur at sites that are not amenable to aspiration (eg mid-foot joints).

Long-term management

Once the acute attack has resolved, long-term management aims to reduce the level of SUA below the saturation point,

preventing further crystal formation and encouraging dissolution of existing MSU crystals, thereby preventing further acute attacks, formation of tophi and joint damage. This is best achieved by a combination of non-pharmacological (education, information access and lifestyle change) and pharmacological measures.

Modification of risk factors, including lifestyle

Recent prospective epidemiological studies confirm that obesity, a purine-rich diet and excess consumption of beer and spirits are independent risk factors for the development of hyperuricaemia and gout.[1] Weight loss and restriction of, but not total abstinence from, dietary purines (red meat and seafood) and alcohol (especially beer) should be advised where appropriate.[3,4] Although other dietary factors, such as fructose and sugar-sweetened soft drinks (increased risk) and cherries, dairy, vitamin C and coffee (reduced risk), are suggested to influence the risk of developing hyperuricaemia and gout,[1] evidence for intervention is insufficient to support modification of these factors in clinical practice.

Loop and thiazide diuretics are further modifiable risk factors.[1] Consideration of reducing or stopping chronic diuretic use is recommended, although this might not be possible when the indication is cardiac or renal failure rather than hypertension.[3,4]

Urate-lowering therapy

Indications – Considerable debate exists about indications for urate-lowering therapy (ULT). Consensus groups suggest offering ULT to all patients with recurrent acute gout, tophi, radiographic damage, renal insufficiency or uric acid urolithiasis.[3,4] Existing guidelines agree that ULT is not indicated for asymptomatic hyperuricaemia in the absence of clinical gout.[3,4] The precise number and frequency of 'recurrent' acute attacks required to consider ULT is not uniformly agreed, but varies from three or more attacks in a 1-year period[4] to a more general acknowledgement that opinion varies between starting ULT after even the first attack (when crystal load is smaller) to waiting until attacks are frequent and troublesome.[3] Although one in five patients presenting with their first attack will have a second episode within 12 months,[8] patients often do not consult for subsequent attacks because they know how to manage them and might have therapy for acute attacks available on repeat prescription. Hence, practitioners might not be aware of recurrent attack frequency and the opportunity to discuss ULT with the patient might not arise. Therefore, there is a case for initiating a discussion about ULT early on during treatment, including information about the aims of ULT and the likelihood of continuing crystal formation, more frequent attacks and joint damage if hyperuricaemia is left untreated. Initiation of ULT can precipitate gout and it is important to both warn the patient of this and provide prophylactic treatment strategies (see below).

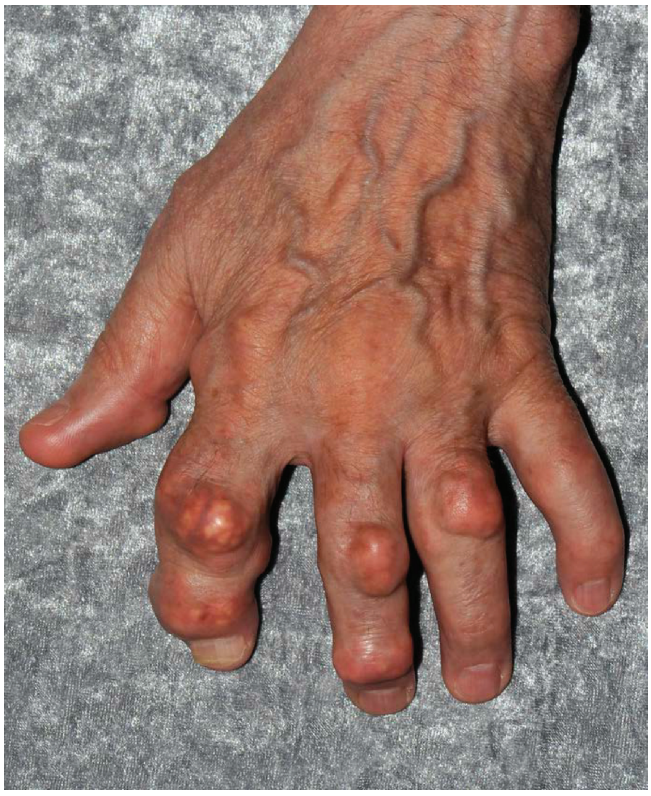

Fig 1. Tophaceous deposits overlying the interphalangeal joints. Note the asymmetrical swelling and yellow-white discoloration of the joints.

Initiation and titration of ULT – The most commonly used ULT is the xanthine oxidase inhibitor allopurinol, which reduces uric acid production (Fig 2). Allopurinol should be initiated at a low dose (usually 100 mg daily) followed by 100 mg increments every few weeks until the target SUA level is achieved. The most conservative target is to reduce the SUA level below 360 μmol/l, which is below the physiological saturation threshold within serum (approximately 380 μmol/l), thereby discouraging new crystal formation, facilitating dissolution of existing crystals and reducing acute attacks.[3,9,10] The British Society for Rheumatology advocates a more stringent target of below 300 μmol/l, based on the observation that the lower the reduced level of SUA, the faster tophi resolve.[4,11] Allopurinol can be titrated, if required, up to a maximum dose of 900 mg daily. Many adults require a dose of 300–500 mg daily to achieve target SUA levels. Allopurinol is usually well tolerated, although infrequent adverse effects include marrow suppression, impaired liver function and rashes. Rarely, a severe life-threatening hypersensitivity reaction can occur, comprising severe skin reactions, fever, renal failure, eosinophilia, hepatitis and leucocytosis. Renal insufficiency is a risk factor for hypersensitivity reactions; thus, it is recommended that lower doses of allopurinol should be used in patients with renal failure and that dose escalation should be more cautious.[3,4] Once the desired SUA level is achieved, it should be monitored every 1–2 years to ensure that it is maintained.

ULT can be particularly challenging in patients who are intolerant of, or have contra-indications (eg azathioprine therapy)

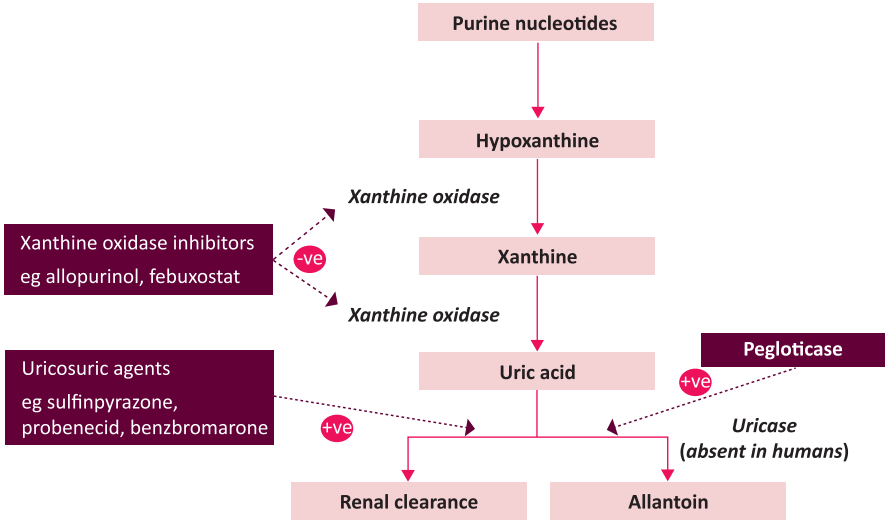

Fig 2. Simplified purine metabolism showing sites of action of urate-lowering agents.

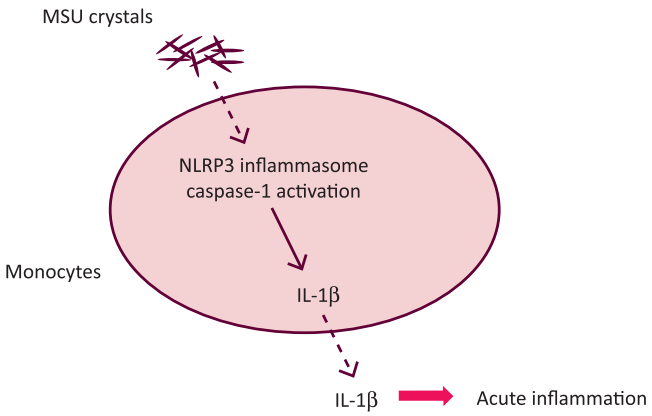

Fig 3. Schematic representation of the detection of monosodium urate (MSU) crystals by the NLRP3 inflammasome. This results in activation of the enzyme caspase 1 and subsequent secretion of ILIL-1β. IL-1β = interleukin 1β; NLRP3 = NLR family, pyrin domain-containing 3; MSU = monosodium urate.

Key points

First-line drugs for treatment of acute gout are a quick-acting oral non-steroidal anti-inflammatory drug (NSAID) or low-dose colchicine (0.5 mg twice to four times daily)

If NSAIDs and colchicine are ineffective or poorly tolerated, corticosteroids are an effective treatment by intra-articular, intramuscular or oral routes

Where appropriate, patients should be advised to lose weight, reduce their consumption of alcohol (particularly beer) and purine-rich foods

Allopurinol should be started at a low dose, for example 50–100 mg daily, and increased slowly with the aim of reducing serum urate to below 360 μmol/l

Options for urate-lowering therapy in patients intolerant of allopurinol include febuxostat, uricosuric drugs or allopurinol desensitisation

KEY WORDS: Hyperuricaemia, gout, therapeutics, allopurinol, colchicine

to, allopurinol or when renal impairment prevents effective dose escalation. A recent advance has been the development of the specific non-purine xanthine oxidase inhibitor febuxostat, which is available at just two doses (80 mg or 120 mg daily).[12] Febuxostat has been approved by the National Institute for Health and Care Excellence (NICE) as a ULT to consider in patients who are intolerant of allopurinol or in whom allopurinol is contra-indicated.[13] It is metabolised by the liver and does not require dose reduction in patients with renal impairment. However, febuxostat is not recommended for use by organ transplant recipients, in the presence of ischaemic heart disease or congestive cardiac failure, or by those taking azathioprine.[14]

Alternative urate-lowering strategies comprise uricosuric drugs, such as sulfinpyrazone, probenecid and benzbromarone, or allopurinol desensitisation. Adverse reactions to allopurinol are more frequent in the presence of renal failure, which also reduces the effectiveness, and increases the renal toxicity, of uricosuric agents. Sulfinpyrazone and probenecid are less effective compared with allopurinol, whereas benzbromarone is a more potent uricosuric drug that can be used in the presence of mild–moderate impairment of renal function, but can rarely cause severe hepatotoxicity. Losartan and fenofibrate (but not other angiotensin II receptor antagonists or fibrates) exert mild uricosuric effects that might appear attractive in patients with concomitant hypertension and hyperlipidaemia, but are less effective in the presence of renal impairment.[15] Uricosuric drugs should be avoided in patients with a history of uric acid urolithiasis. Oral desensitisation to allopurinol can be considered following a mild cutaneous reaction to allopurinol, without features of allopurinol hypersensitivity syndrome, if the patient cannot be treated with other urate-lowering drugs. Allopurinol is started at a very low dose and then escalated very slowly every few days, increasing up to 100 mg daily over a 1-month period.[16]

Preventing ULT-induced acute attacks – Precipitation or worsening of an acute attack of gout can occur following initiation

of any ULT at doses that considerably reduce the level of SUA. Urate lowering leads to partial dissolution of MSU crystals, thus facilitating shedding of crystals into the joint space and triggering acute inflammation. Strategies to reduce this risk include:

- delaying initiation of ULT until the acute attack has resolved,[4] which also enables the patient to be educated about the need for ULT once the painful attack has resolved
- starting ULT at a low dose and slowly escalating the dose to bring about more gradual reductions in SUA and, hence, slower crystal dissolution and less tendency to crystal shedding[3]
- co-prescription of colchicine (500 μg once to twice daily), NSAIDs or corticosteroids when initiating ULT until a stable dose is reached[3,17]
- education of patients to expect an attack of gout after starting ULT, to view this as a sign of successful treatment and not to discontinue ULT if this occurs.

Novel treatment approaches

Recently, there has been interest in the use of biologic agents that inhibit interleukin 1 (IL-1), such as canakinumab, rilonacept and anakinra, to treat acute gout. Following phagocytosis by synovial cells, MSU crystals are detected by the NLR family, pyrin domain-containing 3 (NLRP3) inflammasome, an intracellular receptor within monocytes, where activation of the enzyme caspase 1 leads to secretion of IL-1β and a neutrophilic inflammatory reaction (Fig 3).[18]

In humans, uric acid is the end product of purine metabolism. During the Eocene period, a series of genetic mutations caused higher mammals to lose the ability to produce the enzyme uricase, which converts uric acid to the more soluble allantoin (Fig 2), causing susceptibility to hyperuricaemia. Recent trials have suggested that repeated infusions of pegloticase, a pegylated uricase, are effective at reducing tophi size.[19]

At present, neither of these therapeutic strategies is routinely available in UK clinical practice.

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