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PRACTICE

FROM DRUG AND THERAPEUTICS BULLETIN

Latest guidance on the management of gout

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What you need to know

- An acute attack of gout is likely to require treatment with a NSAID (with gastroprotection for those at high risk of gastrointestinal complications) or colchicine
- In general, urate lowering therapy (ULT) is targeted to patients with recurrent attacks, tophi, urate arthropathy, or renal damage and to symptomatic patients with very high serum uric acid levels. Allopurinal is the first line option
- Shared decision making about ULT should include consideration of harms, benefits, and limitations of ULT, along with patient preferences, comorbidities, and concomitant drug treatments
- All patients taking ULT require regular monitoring of renal function and serum uric acid level to ensure that the dose is appropriate. For many people, allopurinol 300 mg daily will be insufficient to achieve target serum uric acid reductions.
- Despite limited evidence, patients should be encouraged to manage their weight, increase exercise, and reduce alcohol consumption

Gout is the most common inflammatory arthritis and its incidence in the UK has steadily increased from 1.5% in 1997 to 2.5% in 2012.[1 2] It is characterised by deposition of monosodium urate crystals in joints and tissues and usually presents with intermittent painful attacks followed by long periods of remission.[3] Here, we review the latest guidance on the management of gout and consider the role of long term urate lowering therapy.

What are the main risk factors for gout?

The single most important risk factor is sustained hyperuricaemia, which can be caused by overproduction or underexcretion of urate.[2 3] Pathological hyperuricaemia has been defined as the serum uric acid concentration (408 µmol/L) above which monosodium urate crystals form in vitro at physiological pH and temperature. For most people with gout, underexcretion is the main cause of hyperuricaemia. Other factors associated with the development of gout include drugs (such as diuretics, ciclosporin, and low dose aspirin), renal impairment, excessive consumption of red meat or seafood, fructose-sweetened drinks, and alcohol (in particular, beer and spirits).[2-4]

How is it diagnosed?

Although the risk of developing gout increases with higher levels of serum uric acid, hyperuricaemia alone is not sufficient for diagnosis because most people with hyperuricaemia do not have gout.[3 5] However, chronic hyperuricaemia is associated with recurrent flares and can lead to tophi, chronic gouty arthritis, and erosive arthritis.[6] Although a definitive diagnosis of gout is made by the demonstration of monosodium urate crystals in synovial fluid, this is rarely undertaken in primary care.[2]

Is gout associated with particular comorbidities or lifestyles?

There is no consistent evidence that an elevated serum uric acid level results in coronary heart disease, reduced renal function, hypertension, or type 2 diabetes.[3] There is some evidence that a raised serum uric acid level might be associated with worse outcomes in people with cardiovascular and renal disease. So the British Society of Rheumatology recommends that people presenting with gout are assessed for cardiovascular risk factors, including cigarette smoking, hypertension, diabetes, dyslipidaemia, obesity, and renal disease.[2]

Although observational studies suggest an association between dietary factors and gout development, there is no high quality evidence from randomised controlled trials.[7] There is limited evidence that weight loss is associated with a small reduction in serum uric acid levels.[8 9] Guidelines recommend that patients are provided with appropriate lifestyle advice on exercise, weight management, and healthy eating aimed at reducing cardiovascular risk and other related comorbidities.[2 10]

Treatment of acute gout

Treatment for an acute attack should be started as soon as possible.[2 10 11] Non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine are recommended as first line treatment options for an acute attack, with systemic corticosteroids generally

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restricted to those people who don't respond to, or cannot tolerate, NSAIDs or colchicine.[2 10 12]

NSAIDs

Although guidelines recommend using an NSAID for acute gout flares, the authors of a Cochrane review (23 trials, 2200 participants) found limited evidence supporting the use of NSAIDs in the treatment of acute gout.[2 10 11 13 14] However, they noted that the data did not conflict with clinical guideline recommendations that were largely based on observational data, expert opinion, and use in other inflammatory conditions. In terms of pain relief, there was some evidence that systemic glucocorticoids and NSAIDs were equally beneficial.

There are no clinically important differences between NSAIDs in patients with gout.[12] NSAIDs may not be suitable for patients with comorbidities (such as reduced renal function, heart failure, cardiovascular disease, and current or previous gastrointestinal perforation, ulcer, or bleeding). A proton pump inhibitor should be offered to people at high risk of NSAID-related gastrointestinal complications.[2 10]

Colchicine

In a Cochrane review (2 trials, 124 participants)[15] high and low dose colchicine reduced the pain of acute gout, but higher doses were associated with more gastrointestinal adverse effects (diarrhoea 23% *v* 77%; severe diarrhoea 0 *v* 19% in one trial[16]).

Several guidelines recommend using a low dose regimen of colchicine.[10-12] The British Society of Rheumatology (BSR) guideline suggests a dose of colchicine 0.5 mg two to four times daily but recognises that higher doses are often associated with gastrointestinal adverse effects.[2] In the UK, the licensed dose of colchicine is 1 mg followed by 0.5 mg after 1 hour; after 12 hours, treatment can resume with a maximum dose of 0.5 mg every 8 hours until symptoms are relieved with no more than 6 mg per course and at least three days between courses.[17]

In people with moderate renal impairment, a lower starting dose or longer duration between doses is recommended. In patients with normal renal or liver function who are taking cytochrome P450 3A4 inhibitors (such as ritonavir, clarithromycin, itraconazole, ketaconazole, and diltiazem) or p-glycoprotein inhibitors (such as ciclosporin), the dose of colchicine should be reduced by 50% or 75% depending on the interacting drug.[17 18] There have been case reports of myopathy and rhabdomyolysis associated with the use of colchicine in people with renal impairment who were also taking simvastatin or atorvastatin.[2 17]

Corticosteroids

European League Against Rheumatism (EULAR) and BSR guidelines recommend a short course (3–5 days) of an oral corticosteroid (30–35 mg/day prednisolone) in patients unable to tolerate NSAIDs or colchicine.[2 10] Although there is no evidence from randomised trials to support the use of intra-articular corticosteroid injections in acute gout, clinical experience and expert opinion suggests that such injections can be helpful, particularly in for gout affecting a single joint or where comorbidity precludes other treatments.[2 14 19]

In patients where monotherapy is insufficient for treating acute flares, a combination of NSAIDs with either intra-articular corticosteroid, oral steroid, or colchicine may be used.[2]

Interleukin-1 inhibitors

Canakinumab is expensive (£9 928/dose), and effectiveness is marginal according to a Cochrane review.[20 21] The National Institute for Health and Care Excellence (NICE) has not published guidance on canakinumab's use. It is not recommended for use in NHS Scotland or NHS Wales.[22 23]

Reducing the risk of recurrence

When should urate lowering therapy (ULT) be used?

The effectiveness of ULT in preventing gout flares and long term complications is much debated. The updated EULAR and BSR guidelines advise that ULT should be considered and discussed with every patient from the first presentation.[2 10] ULT is recommended for patients with recurrent attacks (two or more a year), tophi, urate arthropathy, or renal impairment. The guidelines also suggest that ULT should be initiated close to the time of first diagnosis in patients who are young (<40 years old), have a high serum uric acid level (≥480 μmol/L), are using diuretics, or have comorbidities (such as renal impairment, hypertension, ischaemic heart disease, or heart failure).[2 10] The recommendation to initiate ULT earlier was based on expert opinion and influenced by epidemiological data that gout was associated with increased mortality from coronary heart disease and renal disease. However, randomised evidence of benefit is lacking.

In contrast, the American College of Physicians guideline advises against initiating long term ULT in most patients after a first gout attack or in patients with infrequent attacks.[12] Only moderate quality observational evidence has shown that patients with lower serum uric acid levels had fewer flares than those with higher levels.

The target level for serum uric acid differs between guidelines. The BSR recommends an initial target of 300 μmol/L.[2] A higher target of 360 μmol/L is advocated when tophi have resolved and the patient remains free of symptoms. EULAR suggests an initial target of 360 μmol/L.[10] Many treated patients do not achieve target serum uric acid reductions.[1]

There is currently insufficient evidence to recommend ULT for asymptomatic people with raised serum uric acid levels.[14]

Which drugs are recommmended?

The main classes of urate lowering drugs are the xanthine oxidase inhibitors, which decrease production of uric acid (such as allopurinol and febuxostat), and uricosuric agents, which increase renal excretion of uric acid (such as sulfinpyrazone and benzbromarone, which is not licensed in the UK).[18] In the UK, uricosuric drugs have a limited role and are usually initiated only by a rheumatologist.[2]

Allopurinol

Allopurinol is recommended as first line therapy when renal function allows.[2 10 14] A Cochrane review (11 studies, 4531 participants)[24] found moderate quality evidence that, compared with placebo, allopurinol (100–300 mg daily) probably does not reduce the number of acute gout attacks but does increase the proportion of people achieving target serum uric acid levels without increasing withdrawals due to adverse effects or serious adverse event rates.

Serum uric acid should be measured before starting allopurinol therapy, and can be measured as frequently as every month to titrate dosage.[2 3] The BSR guideline suggests starting allopurinol 50–100 mg daily, increased in 100 mg increments every four weeks (maximum 900 mg/day) until target serum uric acid level has been achieved.[2] In practice, doses of up to 300 mg of

allopurinol are most commonly prescribed, but they may be inadequate to achieve serum uric acid <300 μmol/L.[25]

A lower dose is recommended for people with renal impairment (see table 1), and it is suggested that serum uric acid and renal function should be monitored every three months in the first year and then annually.[26 27] One recent study suggests that gradual titration of the dose upwards from an appropriate starting dose can help achieve the target serum uric acid, without increasing adverse effects.[28]

Although well tolerated by most patients, allopurinol is rarely (0.1–0.4%) associated with severe adverse effects, including severe cutaneous adverse reaction (SCAR), drug reaction with eosinophilia and systemic symptoms (DRESS), and Stevens-Johnson syndrome.[2] People taking allopurinol should be warned to stop the drug immediately if such a rash occurs and to seek medical advice. BSR recommends that patients of Han Chinese, Korean, or Thai descent should be genetically screened for the HLA-B5801 allele because of an increased risk of severe hypersensitivity reactions to allopurinol.

Febuxostat

Febuxostat is recommended as a second-line agent when allopurinol is contraindicated or not tolerated, or where target serum uric acid cannot be reached.[2 10] Similar hypersensitivity reactions to those seen with allopurinol have been reported for febuxostat and the US Food and Drug Administration is currently investigating preliminary reports of an increased risk of heart related death with febuxostat compared with allopurinol.[29 30]

When to start ULT?

ULT is conventionally started after the initial flare has subsided, but a systematic review of three trials showed that initiation of ULT during an acute flare did not prolong the length or severity of the flare.[31] ULT should not be stopped during gout flares, and American College of Rheumatology guidance supports starting ULT during a flare.[14 25] However, EULAR and BSR guidelines still recommend that ULT is best delayed until inflammation has settled as ULT is better discussed when the patient is not in pain.[2 10]

Prophylaxis should be considered when starting ULT, and, based on the evidence from two recent systematic reviews, BSR recommends colchicine 0.5 mg once or twice daily for up to six months.[2] In patients who cannot tolerate colchicine, a low dose NSAID with gastroprotection may be needed for several months.

Education into practice

- What lifestyle advice do you offer to patients newly diagnosed with gout?
- How comfortable do you feel starting urate lowering therapy after a first attack, considering the conflicting guidance? What could you share with patients?
- To what extent do you discuss the risk of diarrhoea and other gastrointestinal side effects with patients before prescribing colchicine?

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Table

Table 1| Starting dose of allopurinol according to renal function[2]

Estimated GFR (mL/min/1.73 m^2)	Allopurinol starting dose
<5	50 mg weekly
5–15	50 mg twice weekly
16–39	50 mg every 2 days
31–45	50 mg daily
46–60	50 mg and 100 mg on alternate days
61–90	100 mg daily

GFR= glomerular filtration rate