The management of gout: Much has changed

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Background

Gout is a common problem that is increasing in prevalence in Australia. It is associated with many serious comorbidities such as hypertension, chronic kidney disease, obesity, diabetes and cardiovascular disease. Recent changes include the way that older drugs are used, as well as newer therapeutics becoming available or in development.

Objective

The objective of this article is to provide an update on the management of gout.

Discussion

Developments in treatment strategies for gout and newer agents to treat gout are discussed in this article. The salient points include the need to treat gout to a serum urate target, the ability to start allopurinol during acute attacks, the need to treat with prophylactic anti-inflammatory drugs for adequate time periods, and the availability of a new urate-lowering drug on the Pharmaceutical Benefits Scheme (PBS).

Gout is not a new disease, but its management has certainly seen much change in the past five years. It is increasingly being recognised as a serious disease that causes functional disability, increased work absence, and negative economic consequences for the individual and community.[1] Australian research indicates that gout is a significant and increasing problem, with at least 1.5% of the general population affected. A very high prevalence (>10%) of the disease is seen in specific groups, such as elderly men.[2,3] Evidence from Australia and the rest of the world shows that the management of gout is suboptimal, as demonstrated by infrequent serum urate testing, low levels of urate-lowering therapy prescription and, when prescribed, inadequate dosing, resulting in serum urate levels above target.

There have been a number of changes to the management of gout, including dosing strategies of older drugs and availability of newer therapeutics. This review provides an update for practitioners on the management of gout.

Common misconceptions

Gout does not occur only in the great toe (podagra), although this is a common site for the initial episode. It can affect any joint in the body and can even mimic the polyarthritis of rheumatoid arthritis. If inadequately treated, it is a condition that usually progresses rather than regresses. Accumulation of urate in the body occurs as a result of an imbalance in intake or intrinsic urate production and excretion through the kidneys and gastrointestinal tract (GIT). Kidney and GIT excretion is influenced mainly by genetics, although factors such as concomitant medications also play a role.

Gout growing in prevalence and impact

Gout has often been viewed as a nuisance and non-serious condition. It is an important condition for a number of reasons.

First, gout is increasing in prevalence as the world population becomes more overweight and obese.[4]

Second, gout causes significant pain, functional impairment and reduction in work participation. Studies have found that those with gout are absent more often from work and take more sick leave than those who do not have gout.[5] This has an impact not just on the patient but also on their finances, family and community as a whole.

Third, gout is associated with a number of serious comorbidities such as hypertension, diabetes mellitus, ischaemic heart disease, kidney disease and obesity. Therefore, patients who present with gout have a very high chance of another serious and treatable condition that can be screened for and treated. It is important to identify comorbid conditions as they have an impact on the therapeutic options for gout.[6] The therapies used to treat comorbidities also need to be considered carefully. There are treatments that:[1,7]

- raise serum urate (eg thiazide, loop diuretics)
- impair the actions of urate-lowering drugs (eg frusemide)
- lower serum urate (eg losartan).

Consideration of potential comorbid conditions, their treatment and their possible impact on gout is therefore critical.

Treat to target

Treating patients to a target serum urate is essential for reducing gout flares and resolving tophi. For those without tophi, a target of <0.36 mmol/L is recommended; for those with tophi, a target of <0.30 mmol/L should be considered.[8] Gout flares decrease with decreasing levels of serum urate. Once the serum urate is below target, gout flares may still occur for up to 12–18 months. They should become more infrequent over time if the serum urate target is maintained, and will stop eventually.

Acute flare treatment

Treatment of acute flares should begin as soon as possible. Non-steroidal anti-inflammatory drugs (NSAIDs) or colchicine are considered first-line agents; oral corticosteroids are reserved for those who cannot tolerate, or who have contraindications, to first-line agents.[9] NSAIDS are typically used at full dose. Colchicine 1.2 mg immediately followed by 0.6 mg six hours later and then 0.6 mg once or twice daily for two to three days for those with normal renal function is often effective (note, the 0.6 mg tablet size is not available in Australia and the 0.5 mg tablet is usually substituted for it).[9] It is not usually associated with the gastrointestinal adverse effects commonly seen with higher doses. Even lower colchicine doses are required for those with renal impairment or receiving CYP3A4 or P-glycoprotein inhibitors.[10] Oral corticosteroids, such as 0.5 mg/kg prednisone for five to 10 days with gradual reduction or an intra-articular steroid injection for those with a monoarthritis due to gout, can be very effective.[9]

Allopurinol should not be stopped during acute flares of gout

Allopurinol should not be stopped during acute flares of gout.[11] Stopping allopurinol during an acute flare means therapeutic effect is lost and the urate level will rise. In addition, there is a real risk of the allopurinol not being recommenced as well as precipitating another flare when it is recommenced.

Allopurinol can be started during an acute attack

Historically, there has been concern that starting urate-lowering therapy such as allopurinol could worsen or prolong the acute gout flare. Two small clinical trials have now found that this is not an issue. Based on these trials, it is reasonable to start allopurinol during an acute flare of gout when combined with acute gout treatment as this does not prolong the flare.[12,13] In addition, it is an ideal opportunity to initiate therapy and educate the patient while they have the acute symptoms, which are a more immediate reminder of the reason for the new therapy.

Allopurinol needs to be started low and up-titrated

Evidence suggests that it is the starting dose of allopurinol, not the maintenance dose, that increases the risk of allopurinol hypersensitivity syndrome (AHS).[14] Therefore, allopurinol should be started at 50–100 mg per day (or less in those with severe renal impairment) and titrated up so patients reach their serum urate target. The American College of Rheumatology recommends that everyone commencing allopurinol start on 100 mg per day, except those with stage 4 or worse chronic kidney disease, where the recommended starting dose is 50 mg per day.[8] It should then be titrated up every two to five weeks, with more caution and longer intervals in those with poorer kidney function.

For example, in a patient with gout, no tophi and normal kidney function, one might start at 100 mg a day for two to three weeks, then increase to 200 mg per day for two to three weeks, then 300 mg per days for two to three weeks.[8] The serum urate should then be checked and, if the target (<0.36 mmol/L) has been reached, the patient can stay on 300 mg per day. If not, the dose is then titrated up to 400 mg per day and the serum urate is checked again. In Australia, the maximum recommended dose of allopurinol is 900 mg.[15]

The risk of AHS is increased in those who carry the HLA-B*5801 allele, which has an increased prevalence in those of Asian descent. Guidelines recommend testing for this allele in high AHS-risk individuals such as people of Asian descent with renal impairment, then avoiding allopurinol if it is present.[8]

Prophylaxis of acute gout flares

Prophylaxis of acute flare of gout is recommended in those commencing on urate-lowering therapy. Gout flares on starting urate-lowering therapy are very common and prophylaxis aims to prevent them from occurring. In a trial of allopurinol where prophylaxis was ceased, a flare rate of 64% was observed.[16] In those receiving naproxen (250 mg twice daily) or colchicine (0.6 mg daily) prophylaxis, 20–28% of patients experienced flares on initiation of urate-lowering therapy.[17] Although no head-to-head trials have been completed, the available data suggest that flare rates are substantially reduced by anti-inflammatory prophylaxis. NSAIDs or colchicine are the first-line recommended agents.[8] This can be achieved by a moderate dose of an NSAID, such as naproxen 250 mg twice daily, or 0.5–1 mg of colchicine per day.[9] Consideration of medication contraindications and use of gastric protection may be appropriate.

The recommended duration of prophylaxis is now longer than what has previously been used. The American College of Rheumatology recommends:

- at least six months' duration, or
- three months' duration after achieving target serum urate in patients without tophi, or

- six months' duration after achieving target serum urate in patients with tophi on examination.

This recommendation is in recognition that even after the target serum urate level has been reached, flares may continue to occur for some time.[8] Every clinical scenario is different and practitioners need to carefully consider the risks and benefits when prescribing prolonged courses of acute gout flare prophylaxis.

Monitoring of serum urate

Once target serum urate has been reached, six-monthly monitoring by testing serum urate is recommended to ensure continuing adequate management and adherence.[8] This includes monitoring serum urate, and checking use of blister packs. Adherence with long-term allopurinol is poor and every effort should be made to encourage patients to continue to take it, including involving family members.

Febuxostat as an alternative urate-lowering therapy

Febuxostat is a newer agent used to treat gout that works by inhibiting xanthine oxidase – the same mechanism as allopurinol. It is now available on the Pharmaceutical Benefits Scheme (PBS) as an 'authority required drug' for patients with gout who have a contraindication to allopurinol or a documented history of AHS, or intolerance to allopurinol necessitating permanent treatment discontinuation.[18] This would therefore be appropriate in patients with allopurinol rash or AHS. In addition, it would be appropriate therapy for those who have HLA-B*5801.

Management of gout in those with severe chronic renal impairment

The evidence guiding the management of those with gout requiring urate-lowering therapy and an estimated glomerular filtration rate (eGFR) <30 mL/min is limited. One approach is to start the patient on a very low dose of allopurinol (eg 1.5 mg per mL eGFR) with very gradual up-titrating (eg 25–50 mg per month). An alternative is the use of low-dose febuxostat, although evidence to support this approach is currently sparse.[19] Referral to a rheumatologist is recommended.

Patient education

Research has suggested that patients with gout who lack confidence in their treatments have reduced adherence to their medications. A lack of confidence in treatment can result from their gout flaring after initiation of urate-lowering therapy.[20] Education about this and other aspects of gout is important to make sure patients understand that although their gout may flare in the short term, they are moving towards a shared goal of no gout attacks in the long term.[21,22] In addition, equipping patients who have gout with the skills and motivation to be adherent with medication is likely to also be very important.

A large intake of sugar or sweetened soft drinks, such as cola or lemonade, is a recognised risk for gout. Patients with gout are advised to limit their intake of these beverages.[8]

Although epidemiological evidence suggests that a high-purine diet increases the risk of gout, there is scant evidence that introducing a low-purine diet in those with gout results in a clinically meaningful reduction in gout flares or serum urate.

A comprehensive approach is best, including providing patients with a schema to help them understand important aspects of gout management (Box 1).

Treatment of asymptomatic hyperuricaemia

No current guidelines or recommendations in the US, UK, Australia or New Zealand support treatment of asymptomatic hyperuricaemia.

Conclusion

The increasing prevalence and impact of gout mean that greater focus is required to ensure best outcomes for patients. Newer therapeutic agents are on the horizon, but gout can still be well treated with our current agents, especially in light of recent insights into treatment strategies, such as commencing allopurinol during acute attacks and starting at a low dose and titrating up. Generally speaking, the most important strategy is to treat to a serum urate target (<0.36 mmol/L in most people) as this is critical to preventing gout flares and resolving tophi.

Box 1. Gout treatment schema[23]

- Set urate target
- Start urate-lowering therapy with prophylaxis
- Ensure patient has acute flare plan (see text for further details)
- Monitor serum urate until target reached
- Titrate urate-lowering therapy to achieve target
- Once target achieved, monitor 6–12 monthly

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