Allopurinol for chronic gout

A Cochrane review found limited evidence from randomised controlled trials to support the efficacy and safety of allopurinol over placebo and other urate-lowering medicines in chronic gout. Significantly more adverse events were reported with allopurinol than febuxostat, but there was no difference in serious adverse events or withdrawal due to adverse events.

Overview: Gout is a disorder of purine metabolism characterised by a raised level of uric acid in the blood (hyperuricaemia) and the deposition of urate crystals in joints (NICE 2012). The presence of crystals causes acute, intermittent and painful attacks of gouty arthritis in the joints, usually the foot (especially the big toe), knee, hand or wrist. In chronic gout, the joints are affected by subcutaneous concentrations of urate crystals (nodular tophi). Renal damage and kidney stones may also occur.

The estimated prevalence of gout in the UK is 1.4% (Mikuls et al. 2005). Around 72% of people with gout in the UK experience at least 1 gout flare annually. The frequency of flares is associated with serum uric acid levels.

Current advice: The NICE Clinical Knowledge Summary on gout advises that acute attacks are usually treated with non-steroidal anti-inflammatory drugs (NSAIDs, with gastroprotection if indicated) or colchicine (second-line treatment). Corticosteroids are an alternative when NSAIDs and colchicine are unsuitable or not tolerated. Lifestyle advice should be offered to all people with gout.

If hyperuricaemia persists despite lifestyle modification and further attacks of gout occur, urate-lowering therapy should be considered. The British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of gout (under review) recommends allopurinol in a starting dose of 50–100 mg/day and adjusting to a maximum dose of 900 mg/day until a serum urate level of less than 0.3 mmol/l (5.4 mg/dl) is reached. Cohort studies have shown that people who achieved plasma urate levels of less than 0.36 mmol/l (6 mg/dl) had a reduced frequency of subsequent gout attacks. Other urate-lowering medicines (such as sulfinpyrazone) are second-line options.

NICE guidance advises that febuxostat is an option for managing chronic hyperuricaemia in gout, but only for people who are intolerant of allopurinol or for whom allopurinol is contraindicated (NICE)
technology appraisal guidance 164). NICE does not recommend pegloticase for treating gout (NICE technology appraisal guidance 291).

The NICE Pathway on musculoskeletal conditions brings together all related NICE guidance and associated products on gout in a set of interactive topic-based diagrams.

New evidence: A Cochrane review by Seth et al. (2014) compared the efficacy and safety of allopurinol with placebo and urate-lowering medicines in 4531 people with chronic gout. It included 11 studies (7 randomised controlled trials [RCTs] and 4 quasi-RCTs) that mostly enrolled males, with gout duration ranging from a few days to 25 years.

In the 2 studies comparing allopurinol with placebo (n=453), participants who received allopurinol 100–300 mg daily were more likely to achieve a target serum urate level than those who received placebo (data could not be pooled due to heterogeneity; moderate-quality evidence). Allopurinol did not perform better than placebo for other outcomes such as reduction in acute gout attacks or pain.

When allopurinol 100–300 mg daily was compared with febuxostat 80 mg daily, 3 studies (n=1136, low-quality evidence) found no significant difference in the incidence of acute gout attacks over 8–24 weeks. However, 4 studies (n=2618, low-quality evidence) provided some disease-oriented evidence of the efficacy of allopurinol compared with febuxostat. More people achieved a target serum urate level of less than 0.36 mmol/l (6 mg/dl) at 6–12 months with febuxostat than with allopurinol (70% with febuxostat 80 mg daily versus 40% with allopurinol 100–300 mg daily; relative risk [RR]=0.55, 95% confidence interval [CI] 0.48 to 0.63, p<0.00001).

In 3 trials (n=2555, moderate-quality evidence), there was no significant difference between allopurinol 100–300 mg daily and febuxostat 80 mg daily in the number of withdrawals due to adverse events or serious adverse events over 24–52 weeks. However, there were significantly more adverse events with allopurinol than febuxostat (RR=1.06, 95% CI 1.01 to 1.12, p=0.022; 4 studies, n=2656) or 120 mg daily (RR=1.12, 95% CI 1.05 to 1.20, p=0.0007; 2 studies, n=1036). The most common adverse event reported with allopurinol was skin rash.

The authors concluded that there was limited RCT evidence to support the efficacy and safety of allopurinol compared with placebo and other urate-lowering medicines. Limitations of this review include that the studies were often at high or unclear risk of bias; comparisons with other clinically relevant drugs were either lacking or from small, single studies; and no studies reported on function, health-related quality of life or participants’ global assessment of treatment success.

Commentary: “Gout is the most common form of inflammatory arthritis diagnosed in men and the only curable form of arthritis. This evidence shows the paucity of good quality clinical trials investigating allopurinol, which is the most commonly used drug to treat gout and has been used in clinical practice since the 1970s.

“Unfortunately allopurinol is rarely used effectively in the UK (Annemans et al. 2008). The principles of ‘treat to target’ (maintaining serum urate levels at less than 0.36 mmol/l [6 mg/dl] long term) and upward dose titration dependent on urate levels are often neglected. If allopurinol was used appropriately, many more patients would achieve long-term cure from their gouty arthritis, resulting in reduced long-term disability from erosive joint disease.

“At face value, the clinical studies discussed by Seth et al. (2014) show that febuxostat is more effective than allopurinol 300 mg daily or lower at reducing serum urate levels to less than 0.36 mmol/l (6 mg/dl). However, this finding was based on evidence considered low quality by the authors. In addition, reduction in serum urate levels is a disease-oriented outcome and less useful than patient-oriented outcomes such as reduction in gout attacks. These results are consistent with NICE guidance that febuxostat is an option for managing chronic hyperuricaemia in gout, but only for people who are intolerant of allopurinol or for whom allopurinol is contraindicated (NICE technology appraisal guidance 164).
“The main anxiety concerning these studies is that higher doses of allopurinol were not trialled. In the rheumatology community, it is widely accepted that doses of allopurinol up to 600 mg daily are likely to be required to reduce serum urate levels to below 0.36 mmol/l (6 mg/dl). Patients increasingly have obesity and polypharmacy compared with the 1970s, when dosing studies suggested allopurinol 300 mg daily was effective at reducing serum urate levels to less than 0.36 mmol/l (6 mg/dl).

“It is unlikely clinical practice will be altered dramatically by this evidence. Hopefully the findings will encourage clinicians to titrate the dose of allopurinol upwards dependent on serum urate level and allow alternative treatment options for patients unable to take allopurinol.” – Dr Kelsey M Jordan, Consultant in Rheumatology and Honorary Senior Lecturer, Brighton and Sussex University Hospitals NHS Trust

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