Prescribing. . .

For Gout Part 2 February 2018

- This month's bulletin looks at the role of urate-lowering therapy (ULT) in people with gout.
- Opinions differ on the effectiveness of ULT in preventing flares and long-term complications.
- Uricosuric drugs increase renal excretion of uric acid and urate-lowering drugs, the xanthine oxidases, decrease its production.
- Over five years there has been 6 % increase in prescribing of these drugs in the Bailiwick.

When should ULT be used ?

The effectiveness of ULT in preventing gout flares and long-term complications is controversial. The updated EULAR and BSR guidelines advise that ULT should be considered and discussed with every patient with a definite diagnosis of gout from the first presentation. It is recommended for patients with recurrent attacks (≥2/year), tophi, urate arthropathy and/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), or who have a high SUA level (≥480 μ mol/L), or are using diuretics and/or have comorbidities (e.g. renal impairment, hypertension, ischaemic heart disease, heart failure).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, DTB in its review has stated that they are not aware of any high-quality randomised controlled trials that have shown that such treatment results in reduced mortality.

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. It notes that the benefits of long-term use (≥12 months) in patients with a single or infrequent gout attacks (<2 per year) have not been studied. Only moderate quality observational evidence from the follow-up of two clinical trials and retrospective cohort studies has shown that patients with lower SUA levels had fewer flares than those with higher levels. The SUA target level differs between guidelines. The BSR recommends an initial target of **300μmol/L**. A higher target of **360μmol/L** is advocated when tophi have resolved and the patient remains free of symptoms. In comparison, EULAR suggests an initial target of **360μmol/L**.However, there is evidence that many patients being treated do not achieve target SUA reductions. There is currently insufficient evidence to recommend use of ULT for people with asymptomatic raised SUA levels.

Choice of ULT

There are two main classes of urate-lowering drugs. The xanthine oxidase inhibitors decrease production of uric acid (e.g. allopurinol, febuxostat) and the uricosuric agents increase renal excretion of uric acid (e.g. sulfinpyrazone, benzbromarone). Uricosuric drugs have a limited role and should ideally only initiated by a rheumatologist.

Details of the monthly dispensing of these drugs via Community Pharmacies in Guernsey and Alderney between 2012 and 2017 are shown below. Allopurinol is the most commonly-prescribed agent, with small numbers on febuxostat. There has been an increase of 6.4% in overall prescribing over 5 years.

Drug	Rxs Dec 2012	Cost Dec 2012	Rxs Nov 2017	Cost Nov 2017
Allopurinol	850	£1,008	906	£818
Colchicine	44	£533	43	£193
Febuxostat	2	£49	9	£219
Sulfinpyrazone	4	£211	0	0
All Gout & Cytotoxic Induced Hyperuicaemia Drugs	**900**	**£ 1,801**	**958**	**£ 1,230**

Allopurinol

Allopurinol is recommended as first-line therapy where renal function allows. A Cochrane review (11 studies, 4,531 participants) compared allopurinol with a range of comparators including placebo and febuxostat over different treatment durations and follow up periods. The authors noted that there was limited high-quality randomised controlled trial evidence for allopurinol. They concluded that in people with chronic gout, moderate-quality evidence indicated that, compared with placebo, allopurinol (100–300mg daily) probably does not reduce the number of acute gout attacks, but does increase the proportion of people achieving target SUA levels, without increasing withdrawals due to adverse effects or serious adverse event rates. SUA should be measured before starting allopurinol therapy, and can be measured as frequently as every month to titrate dosage.The BSR guideline suggests starting allopurinol 50–100mg daily, increased in 100mg increments every 4 weeks (maximum 900mg/day) until SUA target has been achieved. In practice, doses of up to 300mg of allopurinol are most commonly prescribed, but may be inadequate

to achieve SUA <300μmol/L. Allopurinol monotherapy at doses of 300mg daily or less failed to achieve SUA <300μmol/L or <360μmol/L in more than half of subjects with gout. A lower dose is recommended for people with renal impairment and it is suggested that SUA and renal function should be monitored every 3 months in the first year and then annually. Previous recommendations were to dose allopurinol according to creatinine clearance, but this seldom resulted in adequate reduction of SUA nor a reduction in frequency of allopurinol hypersensitivity. More recently, a study recruited patients who had been started on dose of allopurinol appropriate to the level of renal function and compared the effect of gradually titrating the dose upwards with a control group whose dose was not adjusted. Overall, more than 50% of participants had creatinine clearance <60 mL/min. Reduction of SUA to target levels occurred in more patients in the dose-adjustment group (69% vs. 32%), without any significant difference in the number of adverse effects between the groups. Although well tolerated by the majority of 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 Steven Johnson syndrome. People taking allopurinol should be warned to stop the drug immediately if such a rash occurs and to seek medical advice.

Febuxostat

Clinical trials have shown that febuxostat at doses of 80mg or 120mg daily is more effective than allopurinol at a fixed dose of 300mg daily in lowering SUA below 360μmol/L. However, when DTB reviewed the evidence for febuxostat, they concluded that its efficacy and safety compared with allopurinol in doses titrated up to a maximum of 900mg is currently "not known". Febuxostat is significantly more expensive than allopurinol and is recommended as a second-line agent only when allopurinol is contraindicated or not tolerated, or where target SUA cannot be reached. Similar hypersensitivity reactions to those seen with allopurinol have been reported for febuxostat and the USA FDA is currently investigating preliminary reports of an increased risk of heart-related death with febuxostat compared with allopurinol.

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. ULT should not be stopped during gout flares and American College of Rheumatology guidance supports starting ULT during a flare. However, recent 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. Prophylaxis should be considered when starting ULT, and based on the evidence from two recent systematic reviews, BSR recommends colchicine 500mg once or twice daily for up

to 6 months. In patients who cannot tolerate colchicine, a low-dose NSAID with gastroprotection may be needed for several months.

In conclusion

- Gout is a common cause of pain and disability, which is increasing in incidence and yet is often poorly controlled.
- Although there is limited evidence of the effect of lifestyle interventions on the condition, patients with gout should be encouraged to manage their weight, increase exercise and reduce alcohol consumption.
- Patients should be supported with information about the disease and its management.
- An acute attack of gout is likely to require treatment with an NSAID (with gastroprotection for those at high risk of gastrointestinal complications) or colchicine.
- Systemic corticosteroids are generally restricted to those who don't respond to a NSAID or colchicine. Intra-articular corticosteroids may be suitable for patients with gout affecting one or two joints.
- The effectiveness of urate lowering treatment (ULT) in preventing gout flares and long-term complications has been subject to much debate.
- In general, ULT is targeted to patients with recurrent attacks, tophi, urate arthropathy, renal damage and symptomatic patients with very high serum uric acid (SUA) levels.
- Although several clinical guidelines advocate offering ULT after one acute flare to reduce the possible long-term complications associated with an elevated SUA level, the evidence for these benefits is lacking.
- The harms, benefits and limitations of ULT should be discussed with the patient and take in to account co-morbidity and concomitant drug treatment.
- When agreement to start ULT has been reached, allopurinol is recommended as first-line and should be titrated to achieve the desired reduction in SUA.
- Febuxostat is a second-line drug and is significantly more expensive than allopurinol.
- All patients on ULT will require regular monitoring of renal function and SUA level to ensure that the dose of allopurinol is appropriate.

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References : Drugs and Therapeutics Bulletin , January 2018, EPACT.net