Current treatment options for acute and chronic gout

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Gout is the only curable form of arthritis, yet only a third of patients with chronic gout are receiving appropriate urate-lowering therapy. Our Drug review discusses the available treatment options and their properties, followed by sources of further information.

Gout is an old disease, the first description goes back to the ancient Egyptians in 2640 BC and was described by Hippocrates as ‘arthritis of the rich’ because of its association with certain foods and alcohol consumption. However, in more recent studies it has been shown that gout associates with higher levels of deprivation.

Gout is also the only curable form of arthritis. A recently published study has shown that 1 in 40 adults in the UK will be affected by gout (prevalence 2.49 per cent, incidence 1.77 per 1000 person years), with greatest incidence between 80–84 years of age. Gout is more common in males than females, with the peak male to female ratio being 15.4 in those aged 30–34.

Prevalence throughout the developed world is increasing.

Risk factors
The most important risk factor for gout is hyperuricaemia and there is a positive correlation between the serum urate level and frequency of gouty attacks. Serum uric acid level reflects dietary intake, de novo synthesis and excretion. Most occurrences of gout are as a result of underexcretion of uric acid. See Table 1 for risk factors.

Diagnosis
Diagnosis is made by appropriate history and examination, and can be confirmed by aspiration of synovial fluid from an affected joint, demonstrating needle-shaped crystals with negative birefringence under polarised light microscopy. It is important to remember that the presence of crystals does not exclude other forms of inflammatory arthritis or septic arthritis.

Further supporting evidence of gout can be obtained from positive family history and a raised serum uric acid level performed between attacks.

Management
Management of gout is split into management of the acute attack and prevention of attacks through reduction of hyperuricaemia.
**Acute treatment**

NSAIDs are the mainstay of treatment for the acute attack and should be given as per current local guidelines with regard to the co-administration of gastroprotective therapy (see Table 2). Studies have demonstrated that any NSAID is equivalent in efficacy in terms of pain relief when administered at equivalent full-strength doses, including the COX-2 inhibitors – eg etoricoxib (Arcoxia). 11,16,17

Colchicine still has a place in acute treatment as well as in the first few months of chronic treatment. It has been demonstrated to reduce the transport uric acid crystals into neutrophils as well as reducing migration of neutrophils into the joint by reduction of interleukin 1 (IL-1) and tumor necrosis factor (TNF) alpha–induced adhesion molecules on neutrophils and endothelial cells.9,17 Colchicine 500µg twice to four times daily, dependent on tolerability, is useful in those for whom NSAIDs would not be appropriate.

Corticosteroids are a third option in acute treatment. Oral, intramuscular or intra-articular preparations are effective. Oral prednisolone 10–30mg for a few days should be sufficient for a single attack or intramuscular methylprednisolone acetate (Depo-Medrone) 80–120mg would be a reasonable course.11,16,18 The advantage of an intramuscular dose is its prolonged duration of action, which will also allow introduction of chronic treatment if appropriate. Intra-articular steroid type and dosage (unlicensed indication) should be directed by local protocols and the joint involved.

A fourth option in acute gout is the use of IL-1 inhibitors such as anakinra and canakinumab (both unlicensed indication) or rilonacept (not available in the UK). Extremely effective in resistant patients they are, however, very expensive and have a higher risk of side-effects.19–21 These agents are given by injection and should only be considered with specialist input.

**Pharmacological measures in chronic management**

In a recent study only a third of patients with diagnosed gout received appropriate urate-lowering therapy (ULT) and even fewer received it within a reasonable timeframe (19 per cent within six months, 27 per cent within one year).3

All patients who have had two or more acute attacks of gout should be offered ULT.

**Prophylaxis**

Without prophylaxis 77 per cent of patients commenced on ULT will suffer from flare-ups. It is vital to minimise the risk of flare-ups in the early treatment of gout as apparent failure of treatment or worsening of the condition is frequently cited as reason for nonadherence with therapy. It is also beneficial to warn patients commenced on ULT that there is a risk of acute flares and explain to them that this is an indication that therapy is successful.

**Urate lowering**

The agents most commonly used as ULT can be split into three categories:
- uricosuric agents (xanthine oxidase inhibitors) – allopurinol and the newer febuxostat (Adenuric)
- uricosuric agents – benzbromarone, sulfinpyrazone and probenecid
- uricolytics.
Uricostatic agents

Allopurinol
Allopurinol has been the primary urate-lowering agent for three decades and remains the most commonly used agent. Allopurinol is effective and has a demonstrable inverse relationship between dose and serum urate level.

Initially commencing at a dose of 100mg daily, serum urate level and renal function should be checked every one or two weeks and dosage titrated upwards to achieve the desired serum urate level, to a maximum of 900mg daily.

It is of note that 98 per cent of patients receiving allopurinol in the UK receive ≤300mg daily, which may indicate that many are receiving subtherapeutic doses and one-third still suffer from acute flares. Of those receiving allopurinol, 23 per cent still have serum urate level >0.36mmol per litre.3,11,22,23 Reduced doses should be used in renal impairment as allopurinol is renally excreted and in cases of allergy it is possible to administer the active metabolite oxypurinol, but there is 40 per cent cross-reactivity.

Side-effects of allopurinol include rash, eosinophilia, hepatitis, vasculitis, bone-marrow suppression, renal impairment and life-threatening hypersensitivity.

Febuxostat
Febuxostat is a selective inhibitor of xanthene oxidase, it undergoes hepatic metabolism and, unlike allopurinol, does not need any dose reduction in renal impairment or moderate hepatic impairment. Well tolerated in general the most commonly seen adverse effects are liver function test (LFT) derangement, diarrhoea, arthralgia and myalgia, flushing, dizziness and tachycardia.

Trials have demonstrated that febuxostat lowers serum urate level effectively; however, more patients discontinued febuxostat than allopurinol due to LFT derangement and acute flares. The majority of those who had tophi experienced resolution of these by the end of the study.27-29

Febuxostat is currently unlicensed for use in patients with heart failure, due to initial suggestions of excess morbidity in this population but further clinical studies are currently awaited investigating this.

Uricosuric agents

These medications increase urate excretion in the kidney and work by inhibition of the URAT1 reuptake transporter. Uricosuric agents are contraindicated in urate nephropathy or in those with a history of renal stones.

All patients prescribed uricosuric agents should be counselled regarding adequate fluid balance and should aim for production of 2 litres of urine daily.

Although urate stone formation is not a common side-effect, the risk of this is greater with more acidic urine so it is sometimes appropriate to alkalise urine; however, the advice of a renal physician should be sought regarding this.

Benzbromarone
Benzbromarone is a highly effective ULT. Doses of between 50–200mg daily are used and generally well tolerated.30 Benzbromarone was withdrawn from general use due to reports of severe hepatotoxicity, therefore it is only available through specialists on a named-patient basis and LFTs should be closely monitored. It no longer has a licence in the UK.

Benzbromarone is effective in moderate renal failure, unlike the other uricosuric agents.

Sulfinpyrazone
Due to adverse reactions, as well as inefficacy in renal impairment, sulfinpyrazone is difficult to use effectively in clinical practice. Adverse effects are similar to those of NSAIDs as sulfinpyrazone inhibits prostaglandin synthesis. Supply problems have led to a reduction in use recently.

Probenecid
Probenecid is rarely used due to supply problems – currently production is limited and it may become unavailable in the future. It is an effective adjunctive to an uricostatic agent but completely ineffective in renal impairment.

Lesinurad
Lesinurad is a new URAT1 inhibitor currently undergoing phase 3 trials. It has been shown to be effective in reducing uric acid levels in trial subjects to the required level (<0.36mmol per litre) at six months compared to placebo. Adverse effects have been shown to include elevation of serum creatinine levels and GI intolerances.31

Uricolytics
Humans lack active uricase due to two independent mutations. It is suggested that this raised antioxidant activity, led to increased intelligence and improved salt retention. Uricase converts urate into the more soluble allantoin, which is much more easily excreted.

Rasburicase
Rasburicase was developed in 1996 and is effective in tumour-lysis syndrome but is not commonly used in gout mainly due to the significant risk of anaphylaxis and decreased efficacy with long-term use due to high allergenicity.32

Figure 1. In tophaceous gout a target serum uric acid level of 0.30mmol per litre is suggested until the tophi have resorbed
Pegloticase (Krystexxa) is a polyethylene glycol (PEG) conjugate of recombinant uricase. PEGylation of uricase prolongs half-life and reduces allergenicity, making it a more viable option for long-term usage in gout. Unfortunately, although licenced in the UK, it was rejected by NICE due to high cost.

Pegloticase causes extreme urate reduction and can, therefore, be useful in refractory gout or for 'debulking' significant tophaceous disease before switching to a longer-term maintenance agent.

Other agents
Both losartan (an angiotensin-II receptor blocker) and fenofibrate (used in dyslipidaemia) have urate-lowering effects. Neither of these agents is licensed for the treatment of gout nor is the urate-lowering property a class effect, but they can be a useful adjunct in those patients who require an antihypertensive or lipid-lowering agent. Losartan inhibits URAT1, though the mechanism of fenofibrate is less clear.

Conclusion
The prevalence of gout is increasing in the UK and the Western World. It is, therefore, becoming even more important to ensure that this increasingly common disease is better understood and better treated.
Alongside initiating treatment sooner to reduce the morbidity associated with this very painful condition, it is vital to use the available drugs more effectively – “treating to target” of <0.36mmol per litre.

It is also important to change the perception of this disease in both the public and professional populations.\textsuperscript{36,37} It is no longer appropriate to consider gout as the ‘disease of the affluent’ or that it is solely related to overindulgence.

References
33. NICE. Pegloticase for treating severe debilitating chronic tophaceous gout. TA291 June 2013.

Declaration of interests
None to declare.

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For each section, one of the statements is false – which is it?

1. Gout is:
   a. most frequently due to underexcretion of uric acid
   b. more common in men than women
   c. a diagnosis that excludes other forms of arthritis
   d. associated with higher levels of deprivation

2. In the acute treatment of gout:
   a. NSAIDs are the mainstay of treatment
   b. colchicine is not useful
   c. oral prednisolone 10–30mg for a few days to a week should be sufficient for a single attack
   d. an IL-1 inhibitor such as anakinra can be very effective in resistant cases

3. When prescribing a uricosstatic agent, remember that:
   a. allopurinol is mainly eliminated by hepatic metabolism
   b. it is likely that many patients are undertreated with allopurinol
   c. febuxostat does not need any dose reduction in renal impairment or moderate hepatic impairment
   d. in clinical trials, more patients discontinued febuxostat than allopurinol due to liver function test derangement and acute flares

4. In the chronic management of gout:
   a. a diet high in meat or seafood should be discouraged
   b. all patients who have had two or more acute attacks of gout should be offered ULT
   c. the target serum uric acid level in nontophaceous gout is ≤0.50mmol per litre
   d. prophylactic therapy should be given for three to six months on initiation of ULT

5. Regarding the use of uricosuric agents:
   a. patients should aim for a fluid intake that produces about 2 litres of urine daily during treatment
   b. lesinurad is a new URAT1 inhibitor undergoing phase 3 trials
   c. the role of sulfinpyrazone is limited by adverse effects and by lack of efficacy in patients with renal impairment
   d. urate stone formation is a common side-effect

6. Other strategies with potential for the treatment of gout include:
   a. inhibition of uricase with pegloticase
   b. adjunctive use of losartan in patients who need an antihypertensive agent
   c. adjunctive use of fenofibrate in patients who need a lipid-lowering agent
   d. encouraging a low fat diet