The modern management of gout

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Abstract

Gout is an inflammatory arthritis characterized by self-limiting but excruciatingly painful acute attacks. These are a consequence of monosodium urate (MSU) crystals being deposited within articular or periarticular tissue. Chronic tophaceous gout can develop after years of acute intermittent gout. Recent discoveries, including the role of the inflammasome and intracellular events demonstrating that pro-inflammatory cytokines, IL-1β, -8 and TNF-α, promote neutrophil influx. Also, genetic advances with the identification of the URAT-1 transporter and genetic variation in SLC 2A9 as a key regulator of urate homoeostasis, have given us deeper understanding of the pathophysiology of gout, and also allow for more targeted treatments. Hopefully, new and emerging therapeutic options will reduce treatment-resistant gout in patients who are unresponsive or unable to take traditional urate lowering therapy. The development of new therapies may also increase patient numbers being treated in the specialist setting, which may have several secondary benefits.

Key words: Gout, Hyperuricaemia, Treatment, Allopurinol, Febuxostat, Benzbromarone, Inflammasome, URAT-1.

Introduction, definition and epidemiology

Gout was first identified by the Egyptians in 2640 BC, and is one of the oldest recognized diseases. Hippocrates described it as ‘arthritis of the rich’ due to association with certain foods and excessive alcohol [1]. The UK prevalence is 1.4%, which does not appear to be rising [2, 3], in contrast to the worldwide trend [4–6] most notably in America, where the incidence and prevalence have doubled over the past few decades [7].

Gout is an inflammatory arthritis characterized by self-limiting but excruciatingly painful acute attacks. These are a consequence of monosodium urate (MSU) crystal deposition within articular or periarticular tissue. After years of acute intermittent gout, chronic tophaceous gout can develop. Tophi, nodular masses of uric acid (UA) crystals, can form anywhere but most commonly affect finger tips or hands. Recent advances in understanding of intracellular events have occurred along with new treatment development.

Both the British Society of Rheumatology (BSR) [8] and the European League against Rheumatism (EULAR) [9] have recently published gout treatment guidelines. They differ in target serum UA (sUA); ≤0.30 mmol/l for BSR and ≤0.36 mmol/l for EULAR (6 mg/dl), but share the same therapeutic goal of keeping sUA lower than the saturation point of MSU (≤0.36 mmol/l), which prevents crystal formation [10]. The key points of the guidelines are incorporated into this article along with newer discoveries.

Risk factors

Hyperuricaemia is the most important risk factor for developing gout and there is a positive correlation between sUA level and frequency of attacks [2, 11, 12]. However, not all with hyperuricaemia develop gout, and it can occur with normal sUA. sUA levels reflect a balance between dietary intake, synthesis and excretion, with 90% of gout resulting from underexcretion [11]. Causes of primary gout include isolated renal tubular defects in fractional clearance of UA and rare inborn errors of metabolism [13], it is most often found in middle-aged men. Secondary gout occurs in older subjects and is caused by acquired conditions which affect turnover of nucleic acids or renal excretion of uric acid [14], such as myeloproliferative disorders, lymphoproliferative disorders, cytotoxic drugs, fructose ingestion and metabolic syndrome. Risk factors for developing hyperuricaemia are shown in Table 1.

Pathophysiology

Toll-like receptors (TLRs) 2 and 4 in association with adaptor protein MyD33 recognize MSU crystals,
Table 1: Causes of hyperuricaemia

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<td>HPRT: hypoxanthine-guanine phosphoribosyltransferase; PRPP: Phosphoribosylpyrophosphate.</td>
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promoting phagocytosis and subsequent IL-1β production [15]. IL-1β along with pro-inflammatory cytokines, TNF-α and IL-8, promote neutrophil influx, the primary pathological hallmark of gout [15]. Caspases are cysteine proteases that have key roles in cytokine activation. Caspase-1 catalyses IL-1β cleavage from pro-IL-1β [16]. Activation of caspase-1 is regulated by the inflammasome which acts as an intracellular sensor of inflammatory stimuli [16]. A key inflammasome component is the intracellular receptor NALP (NACHT-LRR-PYD-containing protein), which is stimulated following MSU crystal ingestion [15]. MSU crystals also provide a surface for C5 cleavage and complement membrane attack complex formation (C5b-9), which also leads to secretion of pro-inflammatory mediators [15]. Urate crystals interact directly with lipid membranes and proteins through cell membrane perturbation and cross-linking of membrane glycoproteins [11]. This activates several signal transduction pathways including G proteins, phospholipase C and D, which are essential for IL-8 expression, which also promotes neutrophil accumulation [11].

However inflammation is short lived, with neutrophil apoptosis essential for resolution [11]. Monocytes become anti-inflammatory on maturation to macrophages by releasing TGF-β that inhibits IL-1 receptor expression [15]. Proteolytic cleavage, cross-desensitization of chemokine receptors and other anti-inflammatory mediators also contribute to resolution [11].

Further advances in understanding physiology include renal handling of urate. Renal urate transport consists of glomerular filtration, near-complete reabsorption, secretion and post-secretory reabsorption [11]. In 2002, a urate transporter in the human kidney was identified (URAT-1). URAT-1 is a urate–anion exchanger located at the apical brush border of the proximal nephron and a member of the organic anion transporter family (SLC22A12). Drugs such as benzbromarone, sulphinpyrazone and probenecid target this transporter, a mechanism of action not previously understood [17].

A German study later demonstrated that N-terminus polymorphisms of the URAT-1 gene are strongly associated with reduced renal urate excretion and hyperuricaemia [18]. SLC2A9 has been additionally identified as a urate transporter and inheriting one variant of SLC2A9 increases the risk of developing gout by 30–70% (odds ratio = 1.3–1.7) [19]. Interestingly, SLC2A9 also transports fructose and maximal fructose transport occurs in the absence of UA, suggesting a possible mechanism of gene/environment interaction in the pathogenesis of hyperuricaemia and gout [19]. Such advances form the basis of understanding the aetiopathogenesis of gout and may yield future pharmacological targets.

Management

Lifestyle factors

Modification of diet and lifestyle is a core component of gout management. Dietary factors are thought to play a significant role in the increasing prevalence. Obesity is the commonest comorbidity that highlights the importance of addressing diet [2]. Despite long-standing links between diet and gout, only recently have studies described protective or causative components. Higher intakes of alcohol (especially beer) [20], fructose (found in many soft drinks) [21], meat and seafood [22] increase risk, whereas coffee [23], dairy products [22] and low BMI [24] are protective. Both vitamin C [25] and cherries [26] lower sUA levels. Traditionally, patients were advised to adopt low purine diets, avoiding meat, seafood and purine-rich vegetables. Such diets are broadly unappealing and rarely followed. A calorie-restricted diet with low carbohydrate (40% of energy), high protein (30% of energy) and unsaturated fat (30% of energy) [27] should be recommended. Although life style modification is unlikely to significantly reduce sUA, it carries additional benefits in controlling other components of metabolic syndrome associated with gout.

Hyperuricaemia should also trigger assessment for common associated disease, principally those of metabolic syndrome, present in 63% of men with gout [28]. Hypertriglyceridaemia, hypertension, type 2 diabetes, hyperlipidaemia and obesity are the features of metabolic syndrome, which is strongly associated with cardiovascular disease risk. A key physiological change in metabolic syndrome is insulin resistance which decreases renal clearance of UA. Gout is associated with insulin-resistance syndrome, hypertension and hyperlipidaemia [11]. Hyperuricaemia itself may even be an independent risk factor for cardiovascular disease.

Following lifestyle advice, there are three main aspects to gout management; acute flare treatment, depletion of excess UA stores and sUA reduction.
The algorithms summarize the current medical treatment of acute gout (Fig. 1) and chronic treatment (Fig. 2). Products that are currently licensed for the chronic management of gout in the UK are used as the first- and second-line treatments and those that are used on a named patient basis can be used thereafter. National institute of clinical excellence (NICE) guidance has indicated that febuxostat can only be used in patients who have contraindications to, or are intolerant of allopurinol.

**Acute treatment**

The aim of treating attacks is to promptly and safely resolve pain. Joint aspiration is not essential to diagnose acute gout, but remains the gold standard and should be performed if there is any uncertainty in diagnosis or suspicion of sepsis. Joint aspiration is rarely performed in primary care, where the vast majority of gout is seen and managed in the UK [2].

Without treatment, the pain of an acute attack will last for at least a week [29]. Time from treatment to termination is the only guide to judge the efficacy of acute treatments as few placebo-controlled trials exist. In addition to pharmacological agents, affected joints should be rested.

**Chronic treatment**

Lifestyle advice about diet and alcohol intake

Prophylactic cover of colchicine (0.5 mg b.d. for 6 months) or NSAID (low dose for 6 weeks)

Titration of allopurinol up to 900 mg/day against sUA and renal function

Aiming sUA ≤ 0.30 mmol/l

- Contraindication (CI) or AEs and normal renal function
- CI or AEs and abnormal renal function
- Failure to reach target sUA and no CI/AEs

- Febuxostat
- Sulphinpyrazone
- Probenecid

- Benzbromarone

If comorbidities are present use losartan and fenofibrate preferentially

Fig. 1 Algorithm for the medical treatment of acute gout. PPI: proton pump inhibitor.
for 1–2 days and treated with ice which has a significant analgesic effect [30].

**NSAIDs (conventional and COX-2 inhibitors)**

NSAIDs are the most commonly used first-line treatment in an acute flare. Maximum doses of an NSAID should be commenced quickly, tapering 24h after complete symptom resolution [31]. Head to head NSAID studies show few differences amongst agents [15]. NSAIDs have many adverse effects (AEs) and should be avoided in gastrointestinal ulcer disease, bleeding or perforation, renal insufficiency, heart failure and those taking oral anti-coagulants. AEs are increased in the elderly and co-administration of a proton pump inhibitor should be considered. When contemplating NSAIDs, pre-morbid conditions and drug history should be taken into account on an individual patient basis and any current national guidance adhered to.

Studies have compared the efficacy of NSAID and cyclooxygenase (COX)-2 agents in treating acute flares. One randomized control trial compared indomethacin 50mg three times a day and lumiracoxib 400mg once daily, and found no statistical difference in mean pain intensity change from baseline levels over Days 2–7 of a flare [32]. There was an interesting difference in effect on blood pressure (BP); indomethacin increased systolic BP on average by 2.5mmHg, whereas lumiracoxib decreased it by 1mmHg. A previous study comparing indomethacin 50mg three times a day against etoricoxib 120mg once daily also found comparable pain relief. The COX-2 patients experienced fewer drug AEs (P = 0.003) [33]. However, patients with established ischaemic heart disease, cerebrovascular disease and peripheral vascular disease should not be treated with COX-2 agents [8]. COX-2 agents may have a better GI tolerability, but this is lost with aspirin co-administration [15].

**Colchicine**

Colchicine is an alkaloid derived from the autumn crocus (Colchicum autumnale), and first used in the 6th century AD by Alexander of Tralles [1]. The earliest mechanism described is the ability of colchicine to block microtubule assembly in neutrophils reducing phagocytosis and transport of MSU crystals [15]. Colchicine also affects neutrophil migration into joints by reducing adhesion molecules on endothelial cells and neutrophils in response to IL-1 or TNF-α [11]. More recently, it has been demonstrated that colchicine also reduces NALP3 inflammasome-driven caspase-1 activation by microtubule inhibition which decreases MSU delivery [15].

The only placebo-controlled trial of colchicine in acute gout demonstrated its efficacy [34]. Two-thirds of patients improved in 48h compared with a third in the placebo group. However, all patients developed diarrhoea which occurred before analgesic effect. Unpublished data compared higher (4.8mg in total) and lower (1.2mg in total) doses of colchicine in acute flares and found no difference in pain relief but less diarrhoea with the lower dose [35], thus suggesting lower doses are as efficacious.

Other AEs of colchicine include abdominal cramps, nausea, vomiting and rarely bone marrow suppression, neuropathy and myopathy. Colchicine has the narrowest therapeutic window of any gout therapy. Until symptoms are relieved, 500 micrograms should be used two to four times daily with the maximum dose of 6mg per course (www.bnf.org.uk). Reduced dosing in elderly or those with renal or hepatic impairment is imperative. Colchicine is metabolized by CYP3A4 and excreted by p-glycoprotein. Toxicity can be caused by drugs interacting with its metabolism and clearance, which include macrolides, cyclosporin and protease inhibitors [36]. Unpublished data from healthy individuals highlight the important interaction between colchicine and clarithromycin, which increases the plasma elimination half life of colchicine by 233% via p-glycoprotein inhibition [37].

Intravenous colchicine is no longer licensed in the UK and many clinicians advocate an outright ban as it has a 2% mortality rate [38]. No trials have directly compared NSAIDs and colchicine.

**Corticosteroids**

Corticosteroids act on the cytosolic glucocorticoid receptor to alter gene expression. Steroids also have non-genomic effects mediated by the cytosolic glucocorticoid receptor, membrane-bound glucocorticoid receptor and additional interactions with cellular membrane proteins [39]. In gout, corticosteroid can either be given systemically, IV, IM or IA if one or two joints are affected. Corticosteroids are a good alternative where NSAID and colchicine cannot be used or in refractory cases. A study of 27 patients demonstrated that i.m. triamcinolone acetonide 60mg was safe and as effective as indomethacin 50mg three times daily in treating flares. Resolution of all symptoms occurred a day earlier on average in the steroid group [40]. A more recent randomized control trial (RCT) involving 90 patients compared the analgesic efficacy of oral prednisolone (30mg daily for 5 days) plus paracetamol vs oral indomethacin (50mg three times daily for 2 days and 25mg three times daily for 3 days) plus paracetamol [41]. Pain reduction was similar but the steroid group experienced fewer AEs. Similar results were found in a randomized double-blind trial demonstrating that 35mg of prednisolone gives equivalent pain relief to naproxen 500mg twice a day [42]. AEs were very similar between the two agents and a quarter of patients taking steroids would have had contraindications to NSAID. This trial was not part of a recent Cochrane review [43], which found there was inconclusive evidence to judge the efficacy of systemic corticosteroids despite their use in treating flares for over 50 years. Importantly, however, the review found no important safety concerns regarding corticosteroid use. Corticosteroids may have fewer AEs than other acute treatments when used for short term, particularly in the elderly.

**IL-1 inhibitors**

Anakinra, an IL-1 receptor antagonist, is a new treatment in development. The therapeutic basis for this treatment
Chronic management

Currently, no evidence suggests that asymptomatic hyperuricaemia should be treated, although lifestyle advice should be offered. Urate lowering therapy (ULT) is indicated to treat recurrent attacks, arthropathy, tophi, UA renal lithiasis and radiographic evidence of gout [9]. There is currently no defined point at which to initiate ULT. Advice should be offered. Urate lowering therapy (ULT) is indicated to treat recurrent attacks, arthropathy, tophi, UA renal lithiasis and radiographic evidence of gout [9].

The therapeutic goal is to prevent MSU crystal formation by following BSR or EULAR MSU targets of ≤ 0.30 mmol/L or 0.36 ≤ mmol/L. These values within the normal range of 0.20–0.42 mmol/l quoted by most British laboratories and can cause confusion. Sustained control of sUA below target levels gives good long-term clinical outcomes and decreases flare frequency [46]. However, the optimum target of sUA is unknown and could vary in different patient groups.

Prophylaxis

Prophylaxis against acute attacks should be given when ULT is initiated, either with an NSAID or colchicine. If no prophylaxis is initiated, 77% of the patients experience flares in the first 6 months of commencing allopurinol [47]. One must minimize flares on initiation of ULT, as this is a commonly cited reason for non-concordance.

Colchicine provides effective prophylaxis at low dose, and fewer subjects experience diarrhoea as a side effect than at treatment dose. Results from RCT indicate prophylactic colchicine 600 µg twice a day should be used for at least 3 months and up to 6 months upon initiating ULT, as this significantly reduces flare frequency and severity [47]. However, in UK practice colchicine comes as 500 µg tablets and therefore we recommend 500 µg twice daily for patient convenience.

Uricostatic agents, xanthine oxidase inhibitors

Allopurinol. For the past 30 years, allopurinol has been the mainstay of chronic treatment and accounts for 90% of ULT [2]. It is an effective agent and there is a significant inverse relationship between allopurinol dose and sUA [10]. Allopurinol reduces sUA by inhibiting xanthine oxidase (XO) thereby preventing xanthine, a product of purine catabolism, being converted into UA as shown in Fig. 3. It should be commenced at 100 mg daily and increased by 100 mg every 1–2 weeks titrated against sUA and creatinine clearance (maximum dose is 900 mg) [9]. In the UK, however, 97.9% of patients receive allopurinol sUA >0.36 mmol/l [2].

In the open-label study were unable to take other gout medications due to renal impairment, allergies, GI haemorrhage and history of renal stones. Pain decreased by 75% on average after three injections [45]. No side effects were noted during the trial, and clinical examination showed complete resolution in 9/10 patients on Day 3. In addition to anakinra, other IL-1 inhibitors are in development such as rilonacept, which is currently undergoing Phase III trials.

Fig. 3 Summary of the final part of purine metabolism and site of drug action (XO = xanthine oxidase).

Allopurinol requires reduced dosing in renal impairment, this being its route of excretion. Oxpurinol, the active metabolite of allopurinol, is an alternative in allopurinol allergy, but there is a 40% chance of cross-reactivity [49].

Febuxostat is a new agent which selectively inhibits XO independent of the redox state and does not affect other enzymatic pathways in purine/pyrimidine metabolism [50]. Febuxostat is extensively metabolized by conjugation via uridine diphosphate glucuronosyltransferase and to lesser extent by the cytochrome P450 system. No dose reduction in moderate renal impairment (or moderate hepatic impairment) is required [48]. Other advantageous properties include no interaction with warfarin [51] and a safe alternative in patients with allopurinol allergy [52].

Febuxostat appears to be well tolerated, the most common AEs being abnormal liver function tests (LFTs).
Others include diarrhoea, joint-related/musculoskeletal/connective tissue symptoms, flushing, dizziness, confusion, myalgia and tachycardia [48].

A Phase 2 trial demonstrated the efficacy of febuxostat with 56, 76 and 94% of patients achieving sUA <6 mg/dl within 28 days on 40, 80 and 120 mg, respectively [51]. Six patients discontinued the study prematurely, all belonged to the treatment group.

A Phase 3 trial compared febuxostat 80 and 120mg with allopurinol 300 mg for 52 weeks with the same sUA target [53]. The largest reduction in sUA was achieved in those receiving febuxostat 120 mg (P < 0.001); however, more patients in this group discontinued treatment (P = 0.003). The primary end point was reached in 53% of the patients on 80 mg, 62% on 120 mg of febuxostat and only 21% in those receiving allopurinol. However, overall rates of discontinuation were higher in both the groups of patients on febuxostat, most commonly due to deranged LFTs or acute flares.

It is difficult to make a direct comparison on the efficacy of febuxostat in comparison with allopurinol due to the doses used.

Results from a 5-year febuxostat trial are available, providing longer term safety and efficacy results [54]. At 5 years, 93% of the patients achieved the target of sUA <6.0 mg/dl with daily doses between 40 and 120 mg. Twenty-two per cent (n = 26) had palpable tophi and the majority resolved. Efficacy in renal impairment was demonstrated with no significant relationship between renal function and urate-lowering efficacy found. The most common AE leading to withdrawal from the study was reversible LFT derangement. However, the exclusion criteria of not prescribing in subjects consuming over 14 alcoholic drinks a week must be noted. The most frequently encountered serious AE was atrial fibrillation, but this was not attributed to febuxostat. In December 2008 NICE ruled that febuxostat 80 mg could be used in patients intolerant of or with contraindications to allopurinol (http://www.nice.org.uk/Guidance/TA164). It will be available for UK use early in 2010.

Uricosuric agents. These drugs enhance renal clearance of urate and were first introduced at the end of the 19th century [1]. They are used in <15% of gout patients [55]. Benzbroamaron, sulphinpyrazone and probenecid all directly inhibit URAT-1 and therefore reduce urate reabsorption. Uricosurics are contraindicated in urate nephropathy or history of acute nephrolithiasis [56]. An increased fluid input and output is therefore recommended for all patients [8].

UA stone formation is not common; however, the most important risk factor for UA crystallization and stone formation is a low urine pH (<5.5), rather than an increased urinary UA excretion. To prevent a low urinary pH and decrease the risk of nephrolithiasis, one can alkalize the urine using potassium citrate or bicarbonate, with the goal of increasing urine pH to values >6.0, and up to 7.0. Usually, advice from a renal physician should be sought and all patients should be encouraged and instructed about maintaining urine volumes of at least 2 l per day.

**Benzbromaron.** Benzbroamaron is metabolized by cytochrome P450 and was withdrawn from widespread use because of serious hepatotoxicity. It has been estimated that the risk of hepatotoxicity is 1:17 000 taking into account four published cases and 11 cases reported by Sanofi-Synthelabo (Paris, France) [57]. In three of the published cases, it was being used to treat asymptomatic hyperuricaemia and some groups feel that its withdrawal was unwarranted [57, 58].

Benzbroamaron is a highly effective drug with 100% of the patients achieving target urate levels of <6 mg/dl in a trial showing comparable efficacy to allopurinol [55]. Benzbroamaron doses of 50–200 mg daily are used and generally well tolerated, although regular LFT monitoring is essential. Benzbroamaron additionally inhibits SLC2A9 [59], and is the only uricosuric that is effective in moderate renal impairment. It is particularly useful where allopurinol is contraindicated or not tolerated, such as in the management of renal transplant patients [60]. Benzbroamaron has a limited availability following its withdrawal in 2003 by the manufacturer Sanofi-Synthelabo and is unlicensed in the UK, but available from IDIS House on a named patient basis.

A recent RCT compared benzbroamaron with probencid in patients who could not tolerate allopurinol or failed to achieve sUA of <0.30 mmol/l on allopurinol [61]. Twenty-four per cent of the patients were successfully treated with allopurinol 300 mg/day within 2 months. In those who failed on allopurinol and were assigned to the benzbroamaron (200 mg once daily) arm, 92% (n = 24) achieved the sUA target compared with 65% (n = 31) in the probencid 1 g twice a day arm. This suggests that benzbroamaron is a better choice following treatment failure or AEs with allopurinol.

**Sulphinpyrazone.** Sulphinpyrazone inhibits prostaglandin synthesis much like the NSAIDs and therefore its AEs are similar [62] including gastro-intestinal ulceration, acute renal failure, fluid retention and rarely elevation of liver enzymes and blood disorders. Sulphinpyrazone 200–800 mg daily in divided doses is used. It has no efficacy in renal impairment and adverse reactions make its clinical use difficult [57].

**Probenecid.** Probenecid can be effective as an add-in therapy when allopurinol alone is insufficient [63], but is ineffective in renal impairment. Divided doses of 0.50–2.0 g are used but it is rarely utilized due to difficulties with supply.

**Uricolytics.** Humans unlike nearly all mammals have mutations in the genes encoding the enzyme uricase. The human uricase gene underwent two separate mutations that independently resulted in truncation of gene transcription. This decreased uricase function, but may have increased antioxidant activity, increased intelligence and improved the ability of humans to retain salt [13]. The action of uricase converts urate to allantoin,
which is 10 times more soluble and thus more readily excreted [64]. During the past seven decades, there have been numerous attempts to administer uricase; however, it now appears that this exogenous enzyme has been successfully converted into an effective drug [65].

Rasburicase. In 1996, rasburicase was developed by recombinant DNA technique from a genetically modified strain of Saccharomyces cerevisiae. The efficacy of rasburicase in prevention and treatment of tumour lysis syndrome (TLS) has been well demonstrated despite its cost [66]. However, allergenicity and development of antibodies compromise its effectiveness, the risk of which increases with repeated use [66]. Rasburicase is given IV at a dose of 0.20 mg/kg for 5–7 days to treat TLS. There are additional case reports of using rasburicase to successfully treat gout in a renal transplant patient [64] and a patient intolerant of allopurinol [56]. No trials have assessed rasburicase efficacy in gout, but a small study compared monthly and daily regimes [67]. After 6 monthly infusions, sUA decreased from 612.6 ± 162.4 (baseline) to 341.2 ± 91.8 (P = 0.001). Daily infusions did not produce a significantly sustained reduction, and the incidence of hypersensitivity was higher in the once daily group.

Poly(ethylene) glycol–uricase. Poly(ethylene) glycol (PEG)–uricase differs from most PEGylated proteins currently in clinical use as it does not closely resemble any human amino acid sequence [65]. PEGylation forms a covalent link between a protein and PEG, and has the advantageous properties of prolonging half life and decreasing antigenicity [66]. The mean termination half life of PEG–uricase is ~2 weeks compared with 19 h for rasburicase [68].

PEG–uricase is better tolerated IV than by subcutaneous injection, and post-infusion uricase activity increases in a linear fashion up to 8 mg [69]. Phase 1 trials demonstrated that IV administration is superior to subcutaneous administration in achieving more rapid, significant and prolonged lowering of sUA [69]. PEG–uricase reduces or eliminates UA excretion, which is an attractive property potentially benefiting patients with UA nephrolithiasis [70]. Phase 2 trials from 2004 and 2005 showed that the most effective dose is 8 mg every 2 weeks, and the detection of antibodies against PEG–uricase does not appear to limit treatment either by increasing drug clearance, neutralizing treatment, or increasing adverse events [65]. This is contradicted by unpublished pooled data from Phase 2 and 3 trials, which suggested that high titres of anti-PEG–uricase antibodies (>1:7290) and any titre of anti-polyethylene are associated with a poor treatment response and to infusion reactions (but not severity of infusion reactions) [71]. If antibodies limit the efficacy of PEG–uricase, then a next generation could be developed with different coupling of uricase to PEG [65].

The most common AE of PEG–uricase is inducing an acute flare [70] and infusion reactions. Infusion-related events included nausea, vomiting, dizziness, respiratory symptoms, myalgias and rash, but not anaphylaxis [65]. The results of on-going RCTs are not yet available, but PEG–uricase is another potentially powerful agent for treating refractory gout in those who are unable to tolerate other treatments. PEG–uricase is effective in resolving tophi [72] and could have a role in ‘debunking’ tophi in advanced gout before switching to another agent for maintenance treatment [69].

Others. Losartan, an angiotensin II receptor antagonist used for hypertension, and fenofibrate, a fibrirc acid derivative used in hyperlipidaemia, both have uricosuric actions and reduce sUA [1]. The action on sUA is not a class effect for either drug and neither is licensed in treating gout [1]. Losartan inhibits URAT-1 [17], whereas fenofibrate can down-regulate the expression of the inducible COX-2 enzyme, but its exact mechanism is less well understood [73].

This effect of losartan and fenofibrate on sUA is particularly beneficial, given the frequent co-existence of hypertension and hyperlipidaemia with gout. Preferential use of these agents when treating comorbidities of gout is recommended [8]. Together, these agents can decrease sUA by 40%; however, fractional UA clearance is increased by 110% and there is a risk of urolithiasis [74].

Conclusions

Traditionally, gout was viewed as a disease of the privileged, but is increasingly prevalent among the lower socio-economic classes who have high rates of obesity and diabetes. More is now known about which life style factors protect or cause gout. However, despite significant advances in understanding and exciting developments of new treatments, the management of gout remains sub-optimal in primary and secondary care. Several reasons for this exist, with a common theme being treatment initialization by non-specialists. Ninety-three per cent of the patients are treated by non-specialists and less than one-third referred [75]. Treatment from a generalist increases chances of non-concordance when compared with that of a specialist [75]. Concordance is also reduced if other chronic diseases are present [75, 76]. Prescription errors are surprisingly high with errors found in renal impairment, concomitant use of AZA and inappropriate treatment of asymptomatic hyperuricaemia in 26, 25 and 57% of prescriptions, respectively, in the UK [76]. Old age, male gender, polypharmacy and chronic renal failure are factors associated with the treatment for asymptomatic hyperuricaemia.

Allopurinol is rarely titrated against sUA and indeed sUA monitoring is only performed in 14% of the patients [2]. Prophylaxis against flares when commencing ULT is only prescribed for 25% of patients [10] and frequently prematurely stopped, which can result in non-concordance. One would hope that such mistakes could be reduced by closer adherence to guidelines, and by advancing knowledge and awareness of those providing
the majority of care, or by more frequent specialist consultations. Sub-optimal treatment of gout has wider implications for patients due to the growing recognition of renal and cardiovascular consequences of persistent hyperuricaemia [65].

New and emerging therapeutic options should reduce treatment-resistant gout in patients who are unresponsive or unable to take traditional ULT. The development of new therapies may also increase patient numbers treated in the specialist setting, which may have several secondary benefits.

Rheumatology key messages

- Gout is better understood with the discovery of the inflammasone, SLC2A9 and specific lifestyle factors.
- Novel therapies including febuxostat, anakinra and PEG–uricase offer hope to patient groups previously difficult to treat.
- Allopurinol remains as first-line treatment, but is poorly used.

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The modern management of gout


