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Changing paradigms in the management of gout

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Abstract

The incidence and prevalence of gout have increased, as have comorbid obesity, diabetes mellitus, hypertension, chronic kidney and cardiovascular disease. Gout is now the commonest type of inflammatory arthritis despite availability of safe, effective and potentially 'curative' urate-lowering drugs. Modern imaging studies show that gout is a chronic inflammatory crystal deposition disorder even at the first acute attack and they illuminate the need to eliminate urate crystals by continuing reduction of the serum urate below its solubility threshold. Clinical outcomes, adherence to therapy and quality of gout care in primary care and hospital practice can be greatly improved by better use of allopurinol and flare prophylaxis, greater patient engagement, education and follow-up, and by nurse-led models of care that employ a 'treat-to-target' principle (SUA< 360 or 300μmol/l). Advances in understanding the physiology and genetic control of urate transport in the kidney and gut have led to novel, more selective uricosuric drugs, and basic research on mediators of urate crystal-induced inflammation has pointed to alternative therapeutic targets for treating and preventing gout flares. Current guidelines for the management of gout and indications for the use of some more recently introduced drugs; febuxostat, lesinurad, pegloticase and interleukin-1 antagonists are also briefly reviewed.

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Introduction

It has long been understood that gout is a disorder in which prolonged elevation of serum urate (SUA) can lead to crystal deposition of monosodium urate (MSU), tophus formation, chronic arthritis, urolithiasis and kidney disease, as well as to recurrent flares of acute arthritis and bursitis. Yet despite the availability for more than 50 years of safe, effective, relatively inexpensive and potentially 'curative' urate-lowering drugs there has been a global increase in its incidence and prevalence and gout has become the commonest type of inflammatory arthritis. As many as 2.5% of adults in the United Kingdom[1] and 4.0% in the USA[2] are affected and admissions to hospital of patients with gout have increased considerably in Europe and North America.[3–5] Inadequately treated gouty arthritis leads to structural joint damage, physical disability and chronic impairment of health-related quality of life (HRQOL).[6] In addition, gout is frequently associated with co-morbidities[7] such as chronic kidney disease (CKD), obesity, diabetes mellitus, hypertension and cardiovascular disease, and with increased mortality.[8]

Somehow the paradigm of gout as the first chronic rheumatic disease that could be effectively treated, eliminated and even prevented has been 'lost in translation'.

There are a number of reasons why this eminently treatable disorder has grown in incidence, prevalence and severity[9].

Prolonged elevation of SUA above its crystallisation threshold is the major risk factor for developing gout. Rising population levels of SUA are partly attributable to secular increases in ageing, an increasing prevalence of medical co-morbidities and the use of drugs that raise SUA levels, and partly to changes in lifestyle that have led to global increases in obesity[10] and metabolic syndrome. However, current treatment of gout is far from optimal[9,11] and as many as 70% of patients continue to have recurrent gout attacks.[12]

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Treating to target with urate-lowering therapy (ULT)

Elimination of flares and prevention of progressive joint damage requires long-term treatment with ULT to reduce the SUA to below its crystallisation threshold in order to dissolve crystal deposits and prevent further crystal deposition. Yet less than 50% of patients with gout in UK general practice receive ULT[13] and less than half the patients with gout treated with ULT in the USA[14] achieved reductions of SUA to the sub-saturation target level of 360 µmol/l (6mg/dl) recommended in treatment guidelines from the American College of Rheumatology (ACR)[15] and the European League Against Rheumatism (EULAR)[16] (Table 1 and 2; Figure 1). The guideline from the British Society of Rheumatology (BSR)[17] recommends reduction of the SUA to the more stringent target of 300 µmol/l (5mg/dl) as this is associated with more rapid elimination of crystal deposits[18] and the frequency of flares.[19] It may be prudent, however, to avoid prolonged profound hypouricaemia, as low SUA has been associated with a higher prevalence and progression of some neurodegenerative disorders,[20] possibly because soluble urate has antioxidant activity.

Regrettably, the 'treat to target' principle is not recommended in the current clinical practice guideline from the American College of Physicians (ACP)[21] because until recently it was only supported by retrospective studies and trials that used SUA as the primary outcome measure, rather than by direct evidence of reduction of flare frequency and other clinical benefits from randomised controlled trials (RCTs). The ACP guideline recommends 'treatment to avoid symptoms' without monitoring SUA levels. This is essentially how gout is currently managed in primary care with such poor outcomes. Fortunately, there is now evidence from RCTs of ULT[22,23] for clinically meaningful flare reduction and resolution of tophi. Most recently, a landmark UK community-based RCT compared nurse-led care with patient education and a 'treat to target' strategy, with GP-led usual care in over 500 patients with gout over two years.[24] The target SUA of < 360 µmol/l was achieved significantly more often in the nurse-led care group (95% vs 30%) and flares and tophi were 67% and 79% less frequent in the nurse-led 'treat to target' group. Health economic analysis showed that this strategy was cost-effective and could be cost saving after five years. However, nurse-led models of health care are not universally established or available, and alternative approaches with health professionals other than physicians have also been explored. An RCT comparing pharmacist-led care with usual care of patients with gout by primary care physicians showed more frequent reduction of SUA to <360 µmol/l in the pharmacist-led group.[25] The importance of patient education and better understanding of the pathogenesis of gout and the 'treat-to target' principle are also emphasised in guidelines[15–17] and other primary care trials[26,27] aiming to improve adherence, outcomes and the quality of gout care.

Indications for ULT

Management of gout in general practice is frequently limited to treating recurring acute attacks with anti-inflammatory drugs. Treatment with ULT is often only considered after many flares or in patients with evident tophi or chronic arthritis despite emerging evidence from imaging studies with ultrasound and dual energy computed tomography (DECT) that gout is a chronic crystal deposition disease even at the time of the first attack.[28,29] There is a growing consensus that ULT should be discussed and offered to all patients with gout at the time of diagnosis[16,17] and not only to those with recurring flares, an exceptionally high SUA, tophi, chronic arthritis, renal impairment, urolithiasis, a need for continuing diuretic drug use or to patients with gout beginning at a young age. There is however no strong evidence to support the use of ULT in people with asymptomatic hyperuricaemia.

All ULTs are best started at a low dose with titration upwards until the SUA target is reached. Two small trials have shown that allopurinol can be started during a gout flare without aggravating or prolonging the acute attack. An SUA <360 µmol/l (6 mg/dl) should be maintained indefinitely.[16] Unfortunately, when gout is treated with ULT in General Practice, it is usually with a fixed dose of 300 mg/day of allopurinol without titration or monitoring of the SUA[30], and adherence is exceptionally poor.[31,32]

Allopurinol

Allopurinol is a xanthine oxidase inhibitor (XOI) and the recommended first-line ULT.[16,17] Treatment should commence with a low dose of 50–100mg daily and then be increased in 100 mg increments approximately every four weeks until the

Table 1 EULAR 2016 Guideline overarching principles[16]

A	Every person with gout should be fully informed about the pathophysiology of the disease, the existence of effective treatments, associated comorbidities and the principles of managing acute attacks and eliminating urate crystals through lifelong lowering of SUA level below a target level.
B	Every person with gout should receive advice regarding lifestyle: weight loss if appropriate and avoidance of alcohol (especially beer and spirits) and sugar-sweetened drinks, heavy meals and excessive intake of meat and seafood. Low-fat dairy products should be encouraged. Regular exercise should be advised.
C	Every person with gout should be systematically screened for associated comorbidities and cardiovascular risk factors, including renal impairment, coronary heart disease, heart failure, stroke, peripheral arterial disease, obesity, hyperlipidaemia, hypertension, diabetes and smoking, which should be addressed as an integral part of the management of gout

Table 2 Summary of EULAR 2016 recommendations[16]

1	Acute flares of gout should be treated as early as possible. Fully informed patients should be educated to self-medicate at the first warning symptoms. The choice of drug(s) should be based on the presence of contraindications, the patient's previous experience with treatments, time of initiation after flare onset and the number and type of joint(s) involved
2	Recommended first-line options for acute flares are colchicine (within 12 hours of flare onset) at a loading dose of 1 mg followed 1 hour later by 0.5 mg on day 1 and/or an NSAID (plus proton pump inhibitors if appropriate), oral corticosteroid (30–35 mg/day of equivalent prednisolone for 3–5 days) or articular aspiration and injection of corticosteroids. Colchicine and NSAIDs should be avoided in patients with severe renal impairment. Colchicine should not be given to patients receiving strong P-glycoprotein and/or CYP3A4 inhibitors such as cyclosporin or clarithromycin.
3	In patients with frequent flares and contraindications to colchicine, NSAIDs and corticosteroid (oral and injectable), IL-1 blockers should be considered for treating flares. Current infection is a contraindication to the use of IL-1 blockers. ULT should be adjusted to achieve the uricaemia target following an IL-1 blocker treatment for flare.
4	Prophylaxis against flares should be fully explained and discussed with the patient. Prophylaxis is recommended during the first 6 months of ULT. Recommended prophylactic treatment is colchicine, 0.5–1 mg/day, a dose that should be reduced in patients with renal impairment. In cases of renal impairment or statin treatment, patients and physicians should be aware of potential neurotoxicity and/or muscular toxicity with prophylactic colchicine. Co-prescription of colchicine with strong P-glycoprotein and/or CYP3A4 inhibitors should be avoided. If colchicine is not tolerated or is contraindicated, prophylaxis with NSAIDs at low dosage, if not contraindicated, should be considered.
5	ULT should be considered and discussed with every patient with a definite diagnosis of gout from the first presentation. ULT is indicated in all patients with recurrent flares, tophi, urate arthropathy and/or renal stones. Initiation of ULT is recommended close to the time of first diagnosis in patients presenting at a young age (<40 years) or with a very high SUA level (>8.0 mg/dl; 480 µmol/l) and/or comorbidities (renal impairment, hypertension, ischaemic heart disease, heart failure). Patients with gout should receive full information and be fully involved in decision-making concerning the use of ULT.
6	For patients on ULT, SUA level should be monitored and maintained to <6 mg/dl (360 µmol/l). A lower SUA target (<5 mg/dl; 300 µmol/l) to facilitate faster dissolution of crystals is recommended for patients with severe gout (tophi, chronic arthropathy, frequent attacks) until total crystal dissolution and resolution of gout. SUA level <3 mg/dl is not recommended in the long term.
7	All ULTs should be started at a low dose and then titrated upwards until the SUA target is reached. SUA <6 mg/dl (360 µmol/l) should be maintained lifelong.
8	In patients with normal kidney function, allopurinol is recommended for first-line ULT, starting at a low dose (100 mg/day) and increasing by 100 mg increments every 2–4 weeks if required, to reach the uricaemia target. If the SUA target cannot be reached by an appropriate dose of allopurinol, allopurinol should be switched to febuxostat or a uricosuric or combined with a uricosuric. Febuxostat or a uricosuric are also indicated if allopurinol cannot be tolerated.
9	In patients with renal impairment, the allopurinol maximum dosage should be adjusted to creatinine clearance. If the SUA target cannot be achieved at this dose, the patient should be switched to febuxostat or given benzbromarone with or without allopurinol, except in patients with estimated glomerular filtration rate <30 ml/min.
10	In patients with crystal-proven, severe debilitating chronic tophaceous gout and poor quality of life, in whom the SUA target cannot be reached with any other available drug at the maximal dosage (including combinations), pegloticase is indicated.
11	When gout occurs in a patient receiving loop or thiazide diuretics, substitute the diuretic if possible; for hypertension consider losartan or calcium-channel blockers; for hyperlipidaemia, consider a statin or fenofibrate.

IL: interleukin; NSAID: non-steroidal anti-inflammatory drug; SUA: serum uric acid; ULT: urate-lowering therapy

SUA target has been achieved. Most patients reach target levels of SUA with doses of 300 to 400 mg[24,33] and the maximum dose should not exceed 900mg/day. In patients with renal impairment smaller increments of 50mg should be used, but target urate levels should be the same.[34] In patients with renal impairment, concomitant treatment with diuretics and higher starting doses of allopurinol, rather than the degree of renal insufficiency, are risk factors for the rare, but potentially fatal, allopurinol hypersensitivity syndrome (AHS) and should be avoided. Allopurinol should also be avoided in gout patients carrying the variant allele HLA-B*5801 as the risk of severe cutaneous adverse reactions (SCAR) during treatment with allopurinol is greatly increased. Screening of patients of Korean, Han Chinese and Thai descent for HLA-B*5801 before considering ULT with allopurinol is recommended[15,16] because of the high frequency (6–12%) of this allele in these ethnic groups compared with <2% in Caucasian populations. There is evidence that such screening can reduce SCAR in practice.[35]

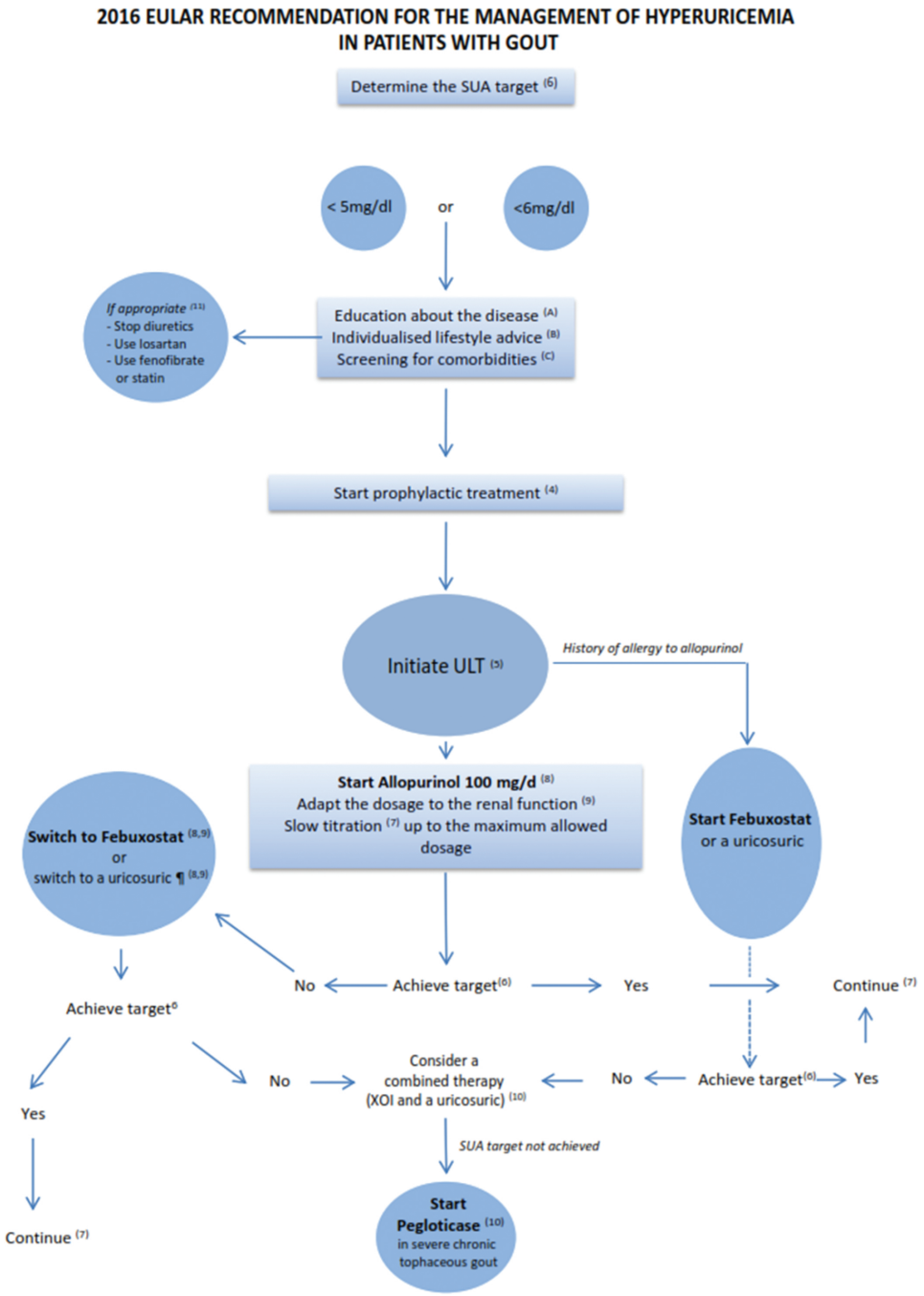

Figure 1 Management of hyperuricaemia in patients with gout according to EULAR recommendations.[16] Letters and numbers in parentheses refer to the items of the recommendations presented in tables 1 and 2 (https://ard.bmj.com/content/76/1/29.long#T1). SUA, serum uric acid; ULT, urate-lowering therapy; XOI, xanthine oxidase inhibitor. At this stage, combined allopurinol and a uricosuric is also recommended.

Febuxostat

Febuxostat is a more selective non-purine XOI which is effective and cost-effective as second-line ULT. Because it is metabolised in the liver, it is often prescribed for patients with renal impairment. It is best started at a dose of 40 mg/day with gradual monthly dose escalation to 80mg/day or 120mg/day to achieve the therapeutic target for SUA, although the summary of product characteristics (SPC) in Europe and the UK recommends 80mg/day as the starting dose. At this dose it is more potent than allopurinol in the most frequently prescribed fixed dose of 300mg/day, but the risk of gout flares following treatment commencement is greater. Apart from very rare case reports of SCAR in patients receiving febuxostat, it is generally well tolerated and can be safely used in patients with a previous history of a mild hypersensitivity rash with allopurinol. There are, however, current concerns and uncertainties about the use of febuxostat in gout patients with co-morbid cardiovascular disease. The US Federal Drugs Administration (FDA) has issued a boxed warning[36] following publication of the results of the large, mandated post-marketing RCT; the Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES) trial.[37] This showed an increase in all-cause mortality and cardiovascular death in the patients treated with febuxostat, although there were no differences in the primary endpoint of major adverse cardiovascular events (MACE). Without a comparator group of patients not being treated with an XOI, it is impossible to know whether allopurinol was actually

differentially protective. Interpretation of the results of CARES is further complicated by the fact that more than half the patients discontinued treatment prematurely, many were lost to follow-up and 85% of the deaths occurred after treatment had been discontinued. The results of a large European Medicines Agency (EMA) mandated post-marketing safety study, the Febuxostat versus Allopurinol Streamlined Trial (FAST),[38] will become available in 2020.

Uricosuric drugs

Uricosuric agents can be used as second-line ULT in patients who are resistant to, or intolerant of XOI, or in combination with them. Although difficult to obtain, sulfinpyrazone (200–800 mg/day) or probenecid (500–2000 mg/day) can be effective in patients with normal or mildly impaired renal function, and benzbromarone (50–200 mg/day) in patients with mild/moderate renal impairment. All uricosurics are contraindicated, or need to be used with great caution, in patients with urolithiasis or severe renal insufficiency.

Recent advances in understanding the genetic control and physiology of urate transport in the kidney and gut have led to the development of new uricosurics and pointed to novel approaches for ULT.

It has been known since the 1950s that most patients with gout are under-excretors of urate with inherently impaired renal capacity to excrete a urate load. In the last decade Genome-wide association studies (GWAS) have identified single nucleotide polymorphisms (SNPs) in numerous loci that are associated with variations in SUA,[39] some of which are also associated with gout. Although only accounting for a small part of the hereditability of gout, four key urate transporter genes have been identified: SLC2A9, which encodes the glucose transporter GLUT9, mediates urate reabsorption into the bloodstream in the basolateral membrane of the proximal renal tubule[40] and SLC22A12, which encodes URAT1, controls urate reabsorption from the urine in the renal tubular apical membrane.[41] NPT1, encoded by SLC17A1, and ABCG2 are secretory urate transporters at this site, ABCG2 is also expressed in the intestine.[42] Uricosuric drugs reduce urate reabsorption predominantly by inhibition of URAT1. Lesinurad is a more selective URAT1 inhibitor which can be used in a dose of 200 mg/day in combination with an XOI for the treatment of hyperuricaemia in patients with gout who have not achieved target SUA levels with an XOI alone,[43] but higher doses and monotherapy should not be used as they can cause renal impairment.

Uricase

Pegloticase is a pegylated mammalian uricase produced in a genetically modified strain of *E.Coli*. It can be used to treat patients with severe disabling chronic tophaceous gout and greatly impaired HRQOL, in whom reduction of SUA to target levels cannot be achieved with any other ULT, or combination of ULTs, at maximal dosages. Pegloticase has been shown to be effective in such patients in two RCTs with improvements in pain, function and HRQOL in addition to reduction in flares, remarkable resolution of tophi and profound reduction in SUA.[23] It is, however, immunogenic despite heavy pegylation. Pegloticase should be administered by IV infusion (8 mg in 250 ml normal saline over two hours) every two weeks by physicians with experience and facilities for dealing with infusion reactions. Pre-treatment with antihistamines and steroids is recommended to reduce the risk of infusion reactions in addition to flare prophylaxis with low-dose colchicine or NSAIDs. SUA should be measured before each infusion and treatment discontinued if the SUA is >360μmol/l as transient responders (about 50%) appear to be at increased risk for infusion reactions and anaphylaxis. Extra caution is required in patients with congestive heart failure and pegloticase is contraindicated in patients with G6PD deficiency because of the risk of haemolysis.

Flare prophylaxis[44]

Initiation of ULT can provoke an increase in the frequency of gout flares. To avoid this leading to poor adherence to ULT, the risk of flares and options for prophylaxis should be fully explained and discussed before starting ULT. Prophylaxis with colchicine 0.5–1mg/day or low-dose NSAID (e.g. naproxen 250mg twice daily) for up to six months is supported by evidence from RCTs and observational studies. Because the risk of flares is related to the speed and degree of SUA reduction, prophylaxis is especially needed in patients starting ULT with febuxostat 80mg/day as this is usually followed by a more rapid and profound fall in SUA than when starting ULT with allopurinol 100 mg/day. Indeed, slow upward titration of allopurinol from this low starting dose can often be accomplished without provoking flares in patients who do not wish to take additional prophylactic drugs.[24]

Despite their widespread use, the efficacy and safety of corticosteroids for flare prophylaxis has not been investigated with RCTs or observational studies. There is, however, some evidence for prophylactic efficacy of interleukin-1(IL-1) inhibitors,[45] although none have regulatory approval for this indication and their cost for prophylactic use is likely to remain prohibitive.

Lifestyle modification

Obesity and heavy intake of meat, seafood, beer, spirits, fructose and sweetened soft drinks are potentially modifiable risk factors for incident gout,[46] and food and alcohol binges are frequent triggers of recurring gout flares.[47] All guidelines for the management of gout emphasise the importance of educating and advising patients about weight and diet [15–17](Table 1), but weight loss and dietary modification have only modest effects in lowering SUA levels[48] and are difficult to sustain. There is, however, some evidence that weight reduction following bariatric surgery in very obese patients can reduce SUA levels significantly,[49] and regular physical activity has been shown to be associated with reduction of mortality in patients with chronic hyperuricaemia.[50] Low-fat dairy products, folate, coffee, and high fibre diets are

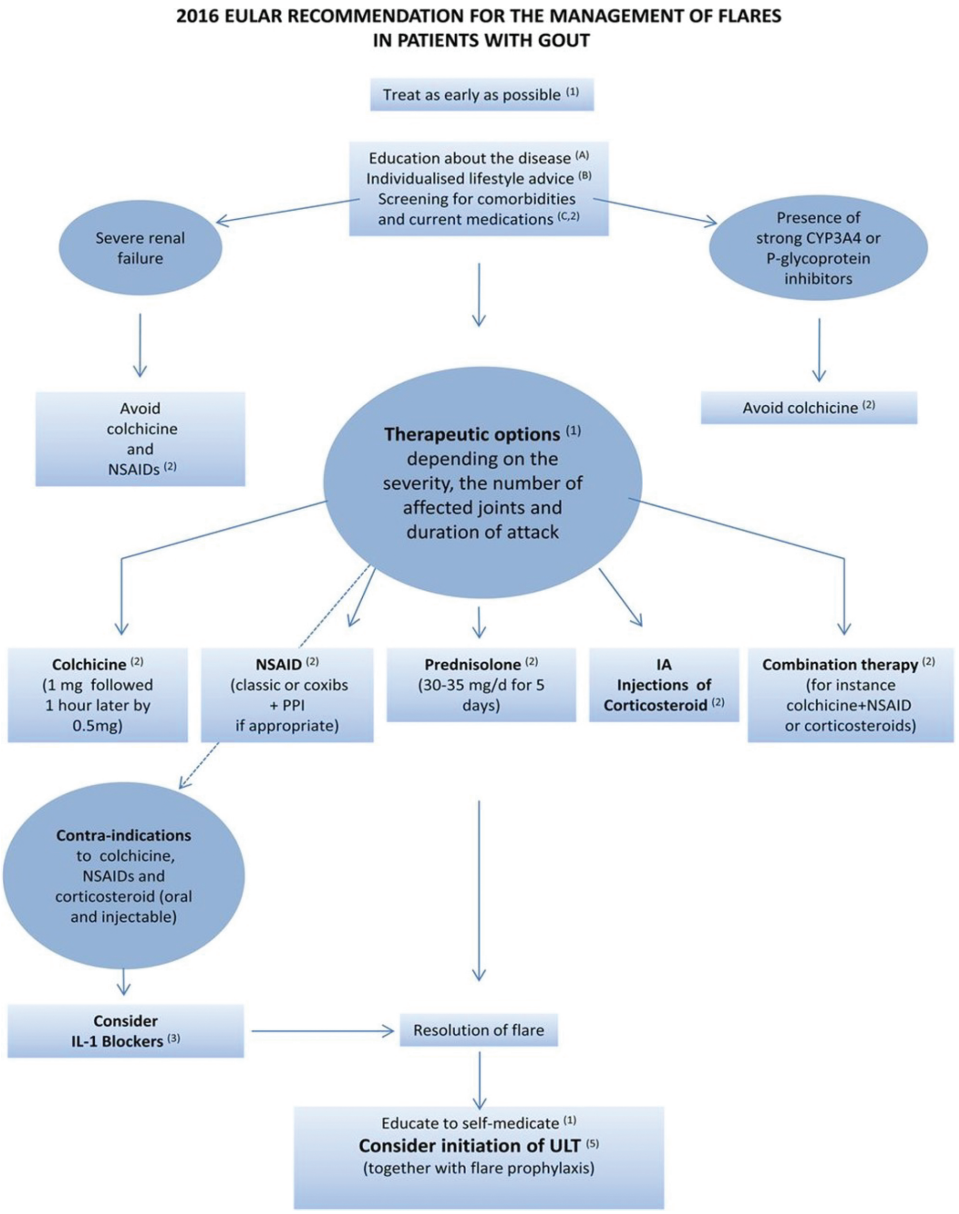

Figure 2 Management of acute flares according to EULAR recommendations.[16] Letters and numbers in parentheses indicate the items of the recommendations presented in tables 1 and II (https://ard.bmj.com/content/76/1/29.long#T1). Strong P-glycoprotein or CYP3A4 inhibitors are cyclosporin, clarithromycin, ketoconazole and ritonavir. IL, interleukin; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; ULT, urate-lowering therapy.

associated with a reduced risk of incident gout and recurrent gout flares,[51] and consumption of cherries or cherry extract can lower the frequency of acute attacks.[52]

Management of gout flares

Recommendations for managing gout flares are summarised in Figure 2 (1–3 in Table 2). Low-dose oral colchicine, NSAIDs with gastroprotection, oral or intra-articular corticosteroids are all options. Without evidence that any is consistently more effective,[53,54] choice is usually determined by the presence or absence of contraindications and individual patient preference. The recently published CONTACT trial of treatment of gout flares in UK general practice found that naproxen (750mg stat followed by 250mg every eight hours for seven days) caused fewer side effects than colchicine (500mcg tds for four days).[54] However, an earlier USA study showed that colchicine 1.2 mg followed after an hour by 0.6 mg was as effective as higher doses of colchicine, with no more side effects than placebo when treatment commenced within 12 hours of symptom onset.[55] Colchicine should not be used in patients with severe renal impairment (GFR <30 ml/min) and with caution and at low doses in patients taking drugs that are potent inhibitors of cytochrome P450 3A4 (CYP3A4) and/or P-glycoprotein (e.g. ciclosporin, cimetidine, clarithromycin, erythromycin, ketoconazole and verapamil). Patients with previous experience of successful management of a gout flare by self-administration of colchicine or an NSAID should be given a supply of the preferred agent to keep at hand with advice to start treatment of any subsequent acute attack as early as possible.

Treatment with combinations of colchicine and NSAIDs or corticosteroids can be considered in patients with very severe, or polyarticular flares.

The evolution of understanding that MSU crystal-induced activation of the NLRP3 inflammasome[56] and production, processing and release of bioactive IL-1 are critically involved in the initiation of gout flares has led to new approaches to treatment and prevention.

IL-1 blockers can be considered in patients with frequent flares and contraindications to colchicine, NSAIDs and corticosteroids. In patients with gout flares and limited treatment options, a single subcutaneous (sc) dose of 150mg of the anti-IL-1β monoclonal antibody canakinumab was more effective than triamcinolone 40mg sc in RCTs.[57] Canakinumab is licenced for use by the European Medicines Agency (EMA) for patients with gout flares and contraindications to colchicine, NSAIDs and corticosteroids but does not have FDA approval. A number of observational studies and one recent RCT have confirmed that the IL-1β receptor antagonist anakinra, 100mg sc on 3–5 consecutive days, can also be effective in patients with severe gout flares.[58,59] Current infection is an important contraindication to the use of all IL-1 blockers and uncertainty about their overall harm and benefits for the treatment of patients with gout are reflected in a Cochrane review.[60]

Direct targeting of NLRP3 with specific small molecule inhibitors is likely to be more cost-effective and less invasive than cytokine blockade[61] and oral administration of dapansutrile has been shown to have promising efficacy for treating gout flares in phase 2 trials.

Comorbidities

The importance of screening for, and appropriate treatment of, renal and cardiovascular co-morbidities and risk factors is emphasised in all current guidelines for gout management[15–17,21] (Table 1) because of their frequency,[1,30] their implications for patients' overall health and survival[8] and their influence on choices of pharmacotherapy for gout. Detection of any comorbid chronic kidney disease (CKD) is particularly important. The EULAR guideline recommends assessing renal function with an estimated glomerular filtration rate (eGFR) at the time of diagnosis and subsequent monitoring of the eGFR with measurements of SUA. The effects of controlling gout and hyperuricaemia on CKD, cardiovascular outcomes and mortality are still inconclusive. Although there is some evidence that allopurinol can slow the progression of renal disease in patients with CKD and hyperuricaemia[62] and that failure to lower the SUA below the target of <360μmol/l in patients with gout receiving ULT is associated with increased cardiovascular mortality,[63] Mendelian randomisation studies do not support the hypothesis that gout or hyperuricaemia directly cause comorbid renal or cardiovascular disease.[64,65]

In patients with gout and hypertension receiving a loop or thiazide diuretic, the possibility of substituting the diuretic with losartan or a calcium-channel blocker should be considered, provided that the blood pressure remains controlled. Losartan and calcium-channel blockers are mildly uricosuric,[66] unlike beta blockers and other angiotensin II receptor antagonists, and their use has been associated with a significantly reduced risk of incident gout in a community-based case-control study.[67] Fenofibrate[68] and statins[69] are also uricosuric and should be considered for the treatment of hyperlipidaemia in patients with gout. Losartan (50mg daily and fenofibrate (300mg daily) have been shown to have additional urate-lowering efficacy in patients with gout treated with allopurinol or benzbromarone.[70]

Low-dose aspirin should be continued when indicated for cardio-protection in patients with gout and cardiovascular disease despite some increase in renal urate retention and a slightly increased risk of gout flares.[71]

Conclusions

Advances in understanding the pathophysiology of gout have led to changing paradigms for the treatment, prevention and elimination of this common crystal arthropathy. Substantial improvements in clinical outcomes in primary care, where most patients with gout are treated, can be achieved by greater patient engagement and education, better use of allopurinol and colchicine or NSAID for flare prophylaxis, and by nurse-led models of care that employ a 'treat to target' strategy of maintaining the SUA< 300 or 360μmol/l. Judicious use of newer agents such as febuxostat, lesinurad, pegloticase and interleukin-1 blockers can improve outcomes for patients with debilitating advanced tophaceous gout, severe renal insufficiency or allopurinol hypersensitivity.

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