REVIEW ARTICLE

Current management of gout: practical messages from 2016 EULAR guidelines

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ABSTRACT

The European League Against Rheumatism published updated recommendations for the management of gout in 2016, comprising 3 overarching principles and 11 key recommendations for clinical practice. Patient education about the pathophysiology of gout and its comorbidities, as well as the existence of effective treatments are important, and understanding the principles of managing acute attacks and eliminating urate crystals by lifelong lowering of the serum urate (SU) below a target level are essential. Advice about lifestyle, diet, weight, and other risk factors, as well as the need to screen for and manage comorbidities are emphasized. For the treatment of flares, colchicine, nonsteroidal anti-inflammatory drugs (NSAIDs), and oral or intraarticular steroids, or a combination thereof, are recommended. In patients with frequent flares and contraindications to colchicine, NSAIDs, and corticosteroids, an interleukin-1 blocker should be considered. Urate-lowering therapy (ULT) should be discussed from the first presentation of the disease, and SU levels should be maintained at less than 6 mg/dl (360 µmol/l), or less than 5 mg/dl (300 µmol/l) in patients with severe gout. Allopurinol is recommended as first-line ULT with dose adjustment according to renal function. If the SU target cannot be achieved with allopurinol, then febuxostat, a uricosuric, or combining a xanthine oxidase inhibitor with a uricosuric should be considered. All ULTs should be started at low dose and titrated upwards until the SU target is achieved. Unless contraindicated, flare prophylaxis with low-dose colchicine or with NSAIDs at low dosage is recommended during the first 6 months of ULT. In patients with refractory gout, pegloticase can be considered.

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Introduction Gout is a chronic crystal deposition disorder in which crystals of monosodium urate can cause chronic arthritis, tophi, urolithiasis and renal disease, as well as recurrent acute arthritis and bursitis. Gouty arthritis and tophi can lead to chronic disability and impairment of health-related quality of life,[1] but gout is also frequently associated with comorbidities such as obesity, diabetes mellitus, hypertension, and cardiovascular disease,[2,3] as well as with increased mortality.[3,4]

The European League Against Rheumatism (EULAR) Standing Committee for International Clinical Studies Including Therapeutics published clinical guidelines for the management of gout in 2006[5] and updated evidence-based expert recommendations in 2016.[6]

With an emphasis on practical messages for patients and physicians, this paper summarizes current EULAR recommendations and indicates where these differ significantly from the earlier guidelines and other recent national and international recommendations for the management of gout.

Why do we need updated recommendations? There were at least half a dozen good reasons why the EULAR recommendations needed to be updated in 2016.

1 Knowledge of the pathophysiology of uric acid (UA) transport, urate crystal inflammation, and the comorbidities associated with gout had advanced considerably.

2 New pharmaceutical options had become available and the evidence base for the efficacy and safety of available drugs had expanded in the last decade.

3 The incidence, prevalence, and severity of gout had continued to increase[7] despite the availability

of safe, effective, and potentially "curative" therapy for more than 50 years.[8]

4 Research studies and audits showed that less than 50% of patients with gout seen in general practice received urate-lowering therapy (ULT)[2,9] and that many patients with gout being treated with ULT in both primary[3] and secondary care[10] did not achieve reductions of serum urate (SU) to the most conservative target level of 360 μmol/l recommended in EULAR and most other guidelines.

5 Attention had been drawn to a range of patient and provider barriers to effective care,[11] and a preliminary proof of principle study had demonstrated that these barriers could be overcome, and outcomes improved, with better provision of information and a package of care based on guideline recommendations.[12]

6 In their 2013 revision of criteria for inclusion of clinical practice guidelines in the United States (US) National Guideline Clearinghouse, the Agency for Healthcare Research and Quality (AHRQ) stipulated that guidelines must have been developed, reviewed, or revised within the last 5 years.[13]

EULAR overarching principles The updated recommendations emphasize 3 overarching principles that are central to the effective management of gout.

Principle 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 the SU level below a target level.

Comment Patient and physician education is essential if patient and provider barriers[11] to effective care are to be overcome. A number of studies have shown that inadequate understanding of the causes and consequences of gout, together with distorted, stereotypical, and generally negative views about gout and its treatment, are associated with lower adherence to ULT and suboptimal disease control.[14-16] A proof of concept observational study has demonstrated that with full patient education, treatment to target with ULT, and nurse follow-up, 98 of 106 patients achieved the therapeutic target, adherence to treatment at 1 year was excellent, and there were improvements in pain and other patient-centered outcomes.[12]

Principle 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.

Comment Lifestyle interventions and dietary modification are frequently a matter of considerable concern to patients with gout. Although their effects on SU levels are small,[17] there is consensus among physicians with expertise and experience in gout that lifestyle education and counselling should be one of the overarching principles of management.

There is some evidence that weight reduction following dietary intervention or bariatric surgery in obese individuals is effective in reducing SU levels,[18,19] and regular physical activity has been shown to be associated with some reduction of the excess mortality in patients with chronic hyperuricemia.[20]

A systematic review of observational studies has confirmed excessive consumption of meat, seafood, alcoholic drinks (especially beer and spirits), sugar-sweetened soft drinks, and fructose-containing foods as significant modifiable risk factors for incident gout,[21] and binge drinking as being associated with an increased risk of recurrent gout attacks, regardless of the type of alcohol consumed.[22] Consumption of low-fat dairy products, folate, coffee, and diets high in dietary fiber are associated with a reduced risk of incident gout and can reduce recurrent gout flares.[23] Fruit and vitamin C supplements (500 mg/d) have only a very modest uricosuric effect,[24] but consumption of cherries or cherry extract can diminish the frequency of acute attacks.[25]

Principle 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 artery disease, obesity, hyperlipidemia, hypertension, diabetes, and smoking, which should be addressed as an integral part of the management of gout.

Comment Screening for comorbidities is advisable because of their frequency,[2,3] their importance for patients' overall health, and the therapeutic implications of their presence for the pharmacotherapy of gout. Detection of chronic kidney disease (CKD) is particularly required, and the EULAR guideline recommends measurement of the estimated glomerular filtration rate (eGFR) at the time of diagnosis followed by subsequent monitoring in parallel with measurements of SU levels. The importance of controlling gout and hyperuricemia, as well as treating comorbidities directly, is highlighted by studies demonstrating that allopurinol slows the progression of renal disease in patients with CKD and hyperuricemia[26] and that gout is an independent risk factor for mortality of CKD and coronary heart disease.[27]

2016 EULAR recommendations The 11 current EULAR recommendations for the management of gout are listed in TABLE 1.

TABLE 1 2016 EULAR recommendations

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 or drugs 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, or an NSAID (plus proton pump inhibitors if appropriate), oral corticosteroid (30–35 mg/d 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 or CYP3A4 inhibitors such as cyclosporine 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 uricemia 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/d, 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 muscular toxicity with prophylactic colchicine. Coprescription of colchicine with strong P-glycoprotein and CYP3A4 inhibitors should be avoided. If colchicine is not tolerated or is contraindicated, prophylaxis with NSAIDs at low doses, 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, or renal stones. Initiation of ULT is recommended close to the time of the first diagnosis in patients presenting at a young age (<40 years) or with a very high SU level (>8.0 mg/dl; 480 µmol/l) and in those with comorbidities (eg, renal impairment, hypertension, ischemic heart disease, or 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, SU level should be monitored and maintained to <6 mg/dl (360 µmol/l). A lower SU 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. SU 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 SU target is reached. SU <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/d) and increasing by 100-mg increments every 2–4 weeks if required, to reach the uricemia target. If the SU 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 is also indicated if allopurinol cannot be tolerated.
9	In patients with renal impairment, the maximum allopurinol dose should be adjusted to creatinine clearance. If the SU 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/1.73 m^2.
10	In patients with crystal-proven, severe debilitating chronic tophaceous gout and poor quality of life, in whom the SU target cannot be reached with any other available drug at the maximum dose (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 hyperlipidemia, consider a statin or fenofibrate.

Abbreviations: CYP3A4, cytochrome P450 3A4; IL, interleukin; NSAID, nonsteroidal anti-inflammatory drug; SU, serum urate; ULT, urate-lowering therapy

Management of gout flares The EULAR recommendations for managing acute gout (1–3 in TABLE 1) are summarized in FIGURE 1.

First-line options are oral colchicine, a nonsteroidal anti-inflammatory drug (NSAID) with gastroprotection, or an oral or intraarticular corticosteroid. Without evidence that any of these are consistently more effective,[28] the choice should be determined by the presence or absence of contraindications and individual patient preference. Fully informed patients for whom an oral agent is appropriate should have a supply of the preferred agent to hand and should be advised to start treatment of an acute attack as early as possible.

The efficacy of colchicine,[29] NSAIDs,[30] and oral corticosteroids[31,32] is supported by a relatively small number of moderate quality randomized controlled trials (RCTs). In a US study, self-administration of colchicine (1.2 mg followed after 1 hour by a dose of 0.6 mg) was shown to be as effective as high-dose colchicine, when taken within 12 hours of symptom onset, with no more side effects than placebo.[33] As colchicine is available in Europe as 0.5-mg rather than 0.6-mg tablets, the EULAR recommendation is for immediate administration of 1 mg followed by 0.5 mg after an hour without further colchicine on the first day, and this can be followed by 0.5 mg once or

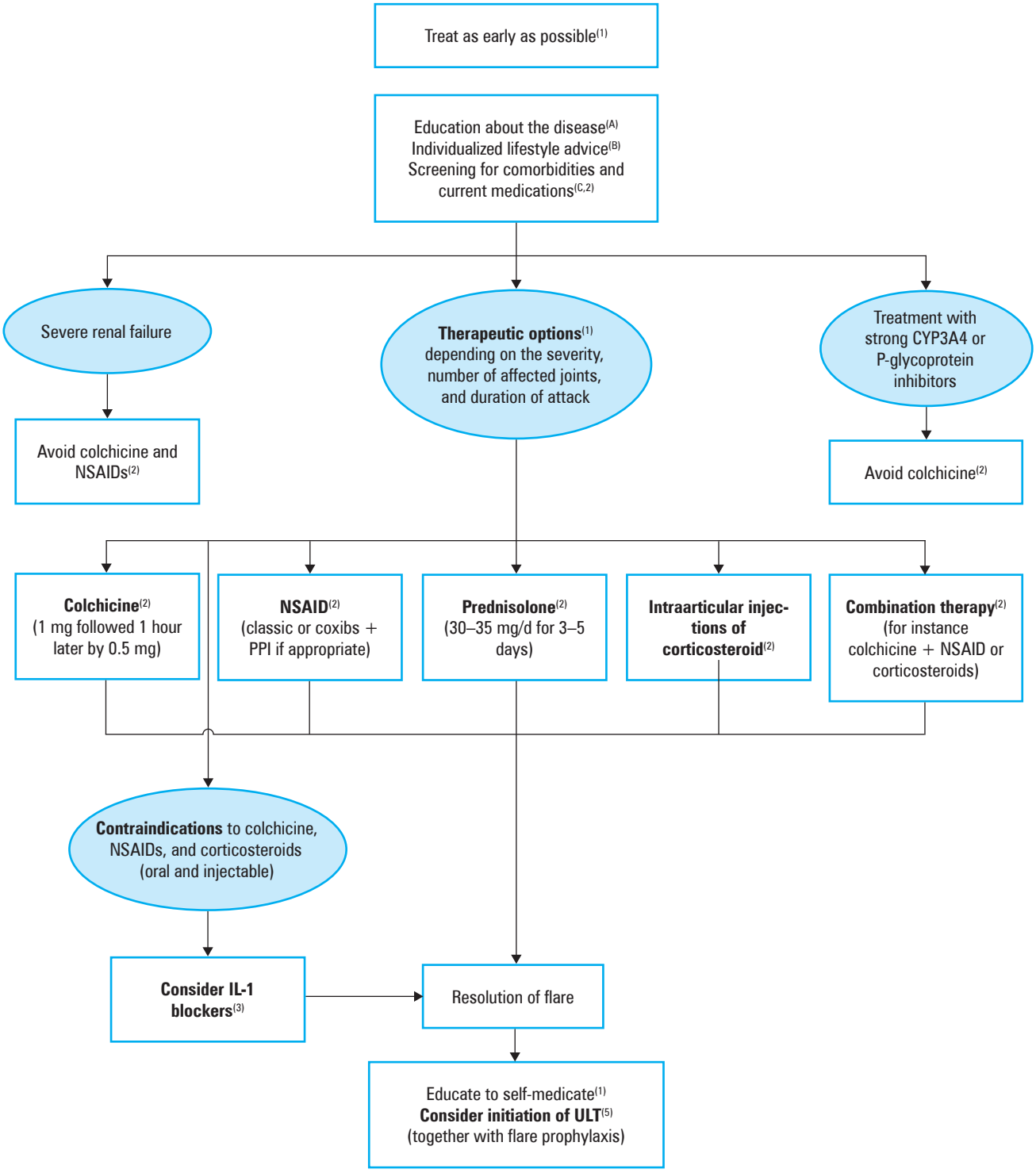

FIGURE 1 Management of acute flares according to EULAR recommendations. Letters and numbers in parentheses indicate the items of the recommendations presented in TABLE 1 and the overarching principles described in the text. Strong P-glycoprotein or CYP3A4 inhibitors are cyclosporine, clarithromycin, ketoconazole, and ritonavir. Modified from Richette et al.[6]
Abbreviations: PPI, proton pump inhibitor; others, see TABLE 1

twice daily, if necessary. Colchicine should not be used in patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2), and should be used with caution and at low doses in patients taking drugs which are potent inhibitors of P-glycoprotein or cytochrome P450 3A4 (CYP3A4) (eg, cyclosporine, cimetidine, clarithromycin, erythromycin, ketoconazole, and verapamil).

Although the efficacy of NSAIDs is supported by only 1 placebo-controlled RCT,[30] numerous head-to-head comparisons have demonstrated that most NSAIDs are equally effective. Because

of the severity of the pain and inflammation associated with acute gout, there is widespread expert consensus that, where there are no contraindications to do so, NSAIDs should be taken at the earliest opportunity, and for a limited period, at high doses. NSAIDs are contraindicated in patients with renal insufficiency, peptic ulceration, or a history of previous upper gastrointestinal hemorrhage or perforation. Selective cyclooxygenase (COX)-2 inhibitors, such as etoricoxib, have equal efficacy and better gastrointestinal tolerability than nonselective NSAIDs,[34] but there are ongoing uncertainties about their relative cardiovascular and renal toxicity with chronic administration.

Oral prednisolone, 30 to 35 mg/d for 5 days,[31,32] and a single intramuscular injection of 7 mg of betamethasone[35] have been shown to have equivalent efficacy with oral NSAIDs for treating gout flares without unacceptable adverse effects. Although only supported by expert opinion, and seldom practical in primary care settings, the EULAR guideline recommends considering intraarticular corticosteroid injection in patients with acute monoarthritis in easily accessible joints.

In patients with very severe, or polyarticular flares, treatment with combinations of colchicine with NSAIDs or corticosteroids should be considered. In patients with frequent flares and contraindications to colchicine, NSAIDs, and corticosteroids, interleukin (IL)-1 blockers should also be considered.

A single subcutaneous (SC) dose of 150 mg of the anti-IL-1β monoclonal antibody canakinumab was more effective than triamcinolone (40 mg SC) in an RCT in such patients.[36] Canakinumab is licensed for use in Europe by the European Medicines Agency (EMA) for patients with gout flares and contraindications to colchicine, NSAIDs, and corticosteroids, but it has not received Food and Drug Administration approval in the US because of uncertainty about its risk-to-benefit ratio. Although not licensed or supported by RCTs for the treatment of gout, observational studies have suggested that the IL-1β receptor antagonist anakinra (100 mg SC on 3 consecutive days) can also be effective in patients with severe gout flares.[37] Current infection is an important contraindication to the use of IL-1 blockers, and ULT should be adjusted to achieve the SU target following treatment of acute gout with an IL-1 blocker. The ongoing uncertainty concerning the overall benefits and harms of IL-1 inhibitors for treating patients with gout are reflected in a Cochrane review.[38]

Flare prophylaxis Initiation of ULT is often followed by an increase in the frequency of acute gout attacks. As this can be an important contributor to poor treatment adherence, the risk of flares and options for prophylaxis should be fully explained and discussed before ULT is started. Recommended prophylaxis with colchicine (0.5–1 mg/d) or a low-dose NSAID (naproxen, 250 mg twice daily) for up to 6 months is supported by evidence from RCTs and observational studies.[39] Patients and physicians need to be aware, however, that there is a risk of neurotoxicity and myopathy with colchicine prophylaxis in patients with renal impairment and in patients receiving statins, so renal function should be assessed before prescribing colchicine or NSAIDs. It is recommended that colchicine prophylaxis should be avoided altogether in patients needing treatment with strong P-glycoprotein or CYP3A4 inhibitors such as cyclosporine, clarithromycin, and erythromycin. As the propensity for flares is related to the speed and extent of SU reduction, prophylaxis is particularly required in patients starting ULT with febuxostat (80 mg/d) as this lowers the SU level to a greater degree than the starting dose of allopurinol (100 mg/d). By contrast, slow upward titration of allopurinol from this low starting dose was accomplished without a significant increase in flares in patients in the Nottingham proof of concept study that chose not to take any drug prophylaxis.[12]

The efficacy and safety of using corticosteroids for flare prophylaxis have not been investigated in RCTs or observational studies. Although there is some evidence for prophylactic efficacy of IL-1 inhibitors,[40] none of them are approved for this indication by the EMA, and it seems likely that the cost of these biologics will always preclude their use for flare prophylaxis.

Management of hyperuricemia The EULAR recommendations for managing hyperuricemia in patients with gout (4–11 in TABLE 1) are summarized in FIGURE 2.

Urate-lowering therapy Treating gout patients with ULT to lower the SU level below its saturation threshold to prevent crystal formation and promote crystal dissolution has been a principle of management for more than 50 years.[8] In the last decade, data from trials and observational studies have shown that prolonged ULT can reduce gout flares[41,42] and tophi[41-43] and improve the quality of life of patients with chronic gouty arthritis.[1,44-46] Treatment of patients with gout and urolithiasis with ULT is supported by observational studies,[47] while the recommendation to consider ULT in patients taking diuretic drugs is supported by cohort and case-control studies which demonstrated higher risks of gouty arthritis in users compared with nonusers of diuretics.[48]

The more recent recommendation to consider treatment with ULT in all patients with gout is based on expert opinion, emerging evidence from imaging studies suggesting that gout is a chronic crystal deposition disease even at the time of the first attack,[49] and studies indicating cardiovascular[50,51] and renal[52] benefits from treatment with xanthine oxidase inhibitors (XOIs). Nevertheless, the EULAR guideline acknowledges a need for further RCTs specifically designed to examine the effects of XOIs on cardiovascular and renal

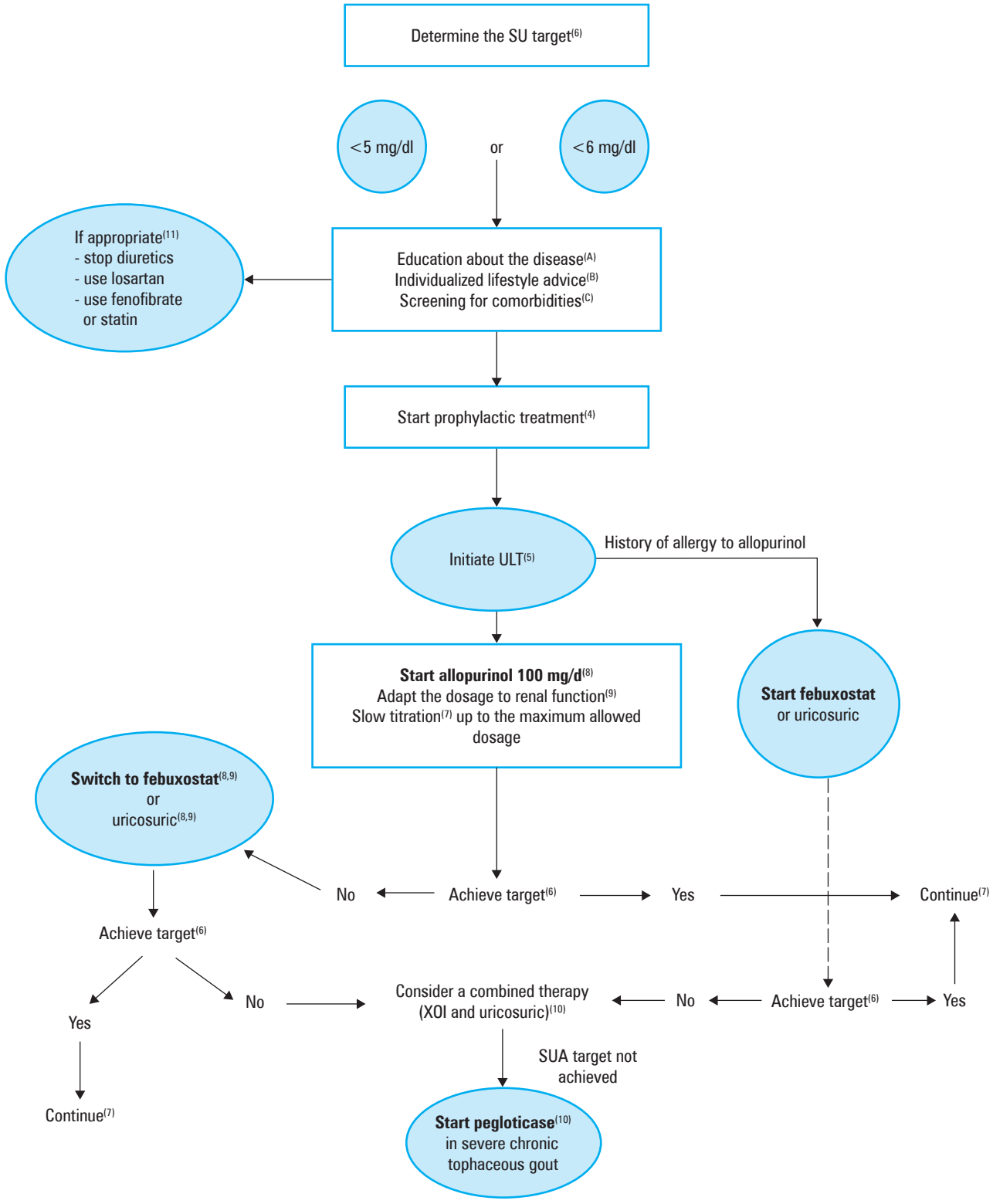

FIGURE 2 Management of hyperuricemia in patients with gout according to EULAR recommendations. Letters and numbers in parentheses indicate the items of the recommendations presented in TABLE 1 and the overarching principles described in the text. At this stage, combined allopurinol and a uricosuric are also recommended. Modified from Richette et al.[6]
Abbreviations: XOI, xanthine oxidase inhibitor; others, see TABLE 1

outcomes as there are also contradictory observational data that did not show cardiovascular benefit or improvement in renal function with XOIs.[53,54] Previous recommendations to delay treatment with ULT drew support from a 1995 health economic study in a Canadian health care setting, which showed that only 62% of patients with nontophaceous gout had a second attack

within 1 year, and that treatment with ULT only became cost-effective (cost saving) in patients suffering more than 3 attacks per year.[55] Additional local and more contemporary studies of this kind could help physicians and patients with gout decide when best to commence ULT. The recommendation to start ULT early in younger patients and in those with high SU (>8 mg/dl or 480 μmol/l) is supported by studies demonstrating younger age as a marker of gout severity[56] and increased frequency of flares with higher SU level.[57] However, the decision as to when to start ULT in any individual should also be influenced by the patient's comorbidities, potential contraindications, drug intolerance or drug interactions, and of course must be ultimately determined by the patient following full explanation and discussion of potential benefits and harms. Treatment with ULTs to lower and maintain the SU level below its saturation threshold in all patients with gout using a treat-to-target strategy is a key guideline recommendation. All ULTs should be started at a low dose and then titrated upwards until the SU target of 6 mg/dl (360 μmol/l) or lower is reached. A lower SU target, of 5 mg/dl (300 μmol/l) or lower, is recommended for patients with frequent flares, chronic arthritis, or clinically evident tophi, in whom the crystal burden is greater, as there is evidence that this will facilitate more rapid crystal dissolution.[58] Subsequent ULT dose reduction to the less stringent target of SU of 360 μmol/l or lower is recommended to avoid further crystal deposition when tophi have resolved and the patient is free from flares.[59] Current advice is to avoid prolonged reduction of SU below 300 μmol/l because of a possible association between low levels and both incidence[60] and progression[61] of Parkinson disease and other neurodegenerative disorders.

The updated EULAR guideline makes no specific recommendation with regard to whether ULT should be initiated during a gout flare despite some evidence that doing so does not increase the severity, or prolong the duration, of acute gout attacks.[62,63] There is, however, widespread consensus that ULT should not be discontinued in the event of a gout flare.[64,65]

Xanthine oxidase inhibitors Allopurinol is the recommended first-line ULT. It should be started at a low dose (100 mg/d) to reduce the risk of precipitating gout flares[12] and rare serious cutaneous adverse reactions (SCARs).[66] The dose should then be increased in 100-mg increments every 2 to 4 weeks until the SU target or maximum dose has been reached. This dose-escalation strategy is safe, effective,[12,67] and cost-effective.[68] The median dose of allopurinol required to achieve the therapeutic SU target of 360 μmol/l or lower in more than 90% of patients was only 400 mg/d,[12] but in general practice less than 50% of patients attain this target with the most widely prescribed dose of 300 mg/d.[3,9] If the SU target cannot be reached with an appropriate dose of allopurinol, allopurinol should be switched to febuxostat or a uricosuric, or combined with a uricosuric.

Although well tolerated by the majority of patients, allopurinol is rarely (0.7/1000 patient years of exposure)[69] associated with potentially life-threatening SCARs including toxic epidermal necrolysis, Stevens–Johnson syndrome, and hypersensitivity drug reactions with rash, eosinophilia, and systemic symptoms; and it is the drug most frequently associated with toxic epidermal necrolysis and Stevens–Johnson syndrome in Europe.[70] Because the risk and the severity of SCARs are increased in patients with impaired renal function,[71,72] the EULAR guideline recommends that in patients with renal insufficiency, the maximum dose of allopurinol should be adjusted to the creatinine clearance (CrCl).[73] If the SU 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 eGFR of less than 30 ml/min/1.73 m^2.

Unfortunately, observational studies have shown that allopurinol dose-adjustment according to CrCl seldom results in adequate reduction of SU levels in patients with gout and renal insufficiency,[74] and a case-controlled study showed no evidence of a reduction in frequency of allopurinol hypersensitivity in patients dosed according to CrCl.[75] Subsequent studies suggested that lowering the starting dose of allopurinol appropriate to the level of renal function reduces the risk of allopurinol hypersensitivity,[66] and that a gradual increase in the dose above the dose based on CrCl resulted in a reduction of SU to target levels in most patients without any increase in toxicity.[76] Although this strategy for using allopurinol in patients with renal insufficiency is endorsed in the American College of Rheumatology (ACR) recommendations,[65] the EULAR task force recommended adhering to the more conservative approach of adjusting the maximum dose of allopurinol to the CrCl[73] because of the potential severity of SCARs, the availability of febuxostat as a therapeutic alternative, and the limited number of patients in the studies of Stamp et al[66] and Seth et al.[67]

Febuxostat is a potent, nonpurine selective XOI, which is effective[45] and cost-effective as second-line ULT.[68,77] As it is metabolized in the liver, it can be used for patients whose renal insufficiency precludes allopurinol dose escalation.[78] It should be started with a dose of 80 mg/d and the dose should be increased, if necessary, to 120 mg/d after 4 weeks to reach the therapeutic target for SU levels. At these doses, it has greater urate-lowering efficacy than allopurinol in its widely used fixed dose of 300 mg/d but the risk of gout flares following initiation of treatment is greater.[45] It is otherwise generally well tolerated, and despite rare case reports of SCARs in patients receiving febuxostat, a previous history of a mild hypersensitivity rash with allopurinol should not

be a contraindication to the use of febuxostat as cross-reactivity does not appear to be a problem.[79]

Uricosurics The uricosuric drugs probenecid (1–2 g/d) and sulfinpyrazone (200–800 mg/d) can be used as alternative ULTs[80] in patients with normal, or only mildly impaired, renal function, who are intolerant of allopurinol, or whose SU is not adequately controlled by an XOI. Benzbromarone (50–200 mg/d) is more potent and can be used in patients with moderate renal impairment (eGFR >30 ml/min/1.73 m^2).[81] All uricosurics are contraindicated or need to be used with great caution in patients with urolithiasis or severe renal impairment. In RCTs in patients who did not achieve target SU levels or tolerate allopurinol at a dose of 300 mg/d, benzbromarone at a dose of 200 mg/d was more effective and better tolerated than 2 g/d of probenecid,[82] and benzbromarone at a dose of 200 mg/d was highly effective and approximately equipotent with allopurinol at a dose of 600 mg/d in lowering SU to target levels.[83] Although generally well tolerated, the use of benzbromarone has been restricted following rare reports of severe hepatotoxicity. Patients treated with benzbromarone should have liver function tests monitored but the risk of serious hepatotoxicity in patients receiving the benzbromarone in Europe is only approximately 1 in 17 000 patients.[84] The EULAR recommendation to consider addition of a uricosuric when treatment with allopurinol alone has failed to lower the SU to target levels is based on observational studies of an effective combination of allopurinol with benzbromarone[85] or probenecid.[86] Since the completion of the 2016 EULAR recommendations, the EMA has granted marketing authorization for the novel uricosuric lesinurad for combination therapy with an XOI for the treatment of hyperuricemia associated with gout in patients who have not achieved SU target levels with an XOI alone. In phase III placebo-controlled RCTs, the addition of lesinurad (200 mg/d) to patients receiving allopurinol (300 mg/d) was safe and effective in increasing the number of patients achieving target SU reduction by 55%,[87] but higher doses and monotherapy are not recommended as they can cause renal impairment.

When gout occurs in a patient receiving a loop or thiazide diuretic for control of hypertension, the possibility of substituting the diuretic with losartan or a calcium channel blocker should be considered, provided that the blood pressure remains controlled. Calcium channel blockers and losartan are mildly uricosuric, unlike β-blockers and other angiotensin II receptor antagonists, and both have been associated with a significantly reduced risk of incident gout in a community-based case-control study.[88] The lipid-lowering agent fenofibrate[89] and statins[90] are also modestly uricosuric and should be considered when prescribing treatment for hyperlipidemia in patients with gout. Losartan (50 mg/d) and fenofibrate (300 mg/d) both had some additional urate-lowering efficacy when administered to gout patients receiving ULT with allopurinol or benzbromarone.[91]

Uricase Pegloticase is a polyethylene glycol modified uricase produced in a genetically modified strain of *Escherichia coli*. It has EMA marketing authorization and is recommended by the EULAR for treating patients with crystal-proven, severe, debilitating chronic tophaceous gout and poor quality of life, in whom the SU target cannot be reached with any other available ULT, or combination of drugs, at the maximum dosage. Two RCTs have shown it to be effective in such patients with improvements in pain, function, and quality of life as well as reduction in flares, tophi, and SU levels,[42] but despite heavy pegylation it is immunogenic. Pegloticase should be given by intravenous infusion (8 mg in 250 ml normal saline over 2 hours) every 2 weeks by physicians with experience and facilities for dealing with infusion reactions. Patients should be pretreated with antihistamines and steroids to reduce the risk of infusion reactions, in addition to low-dose colchicine or NSAIDs for flare prophylaxis. SU levels should be measured before each infusion, and treatment discontinued if, after initial decrease, the SU level exceeds 360 μmol/l as transient responders (about 50%) appear to be at increased risk for infusion reactions and anaphylaxis. Pegloticase is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency because of the risk of hemolysis, and extra caution is required in patients with congestive heart failure.

Alternative recommendations in other contemporary guidelines Most of the 2016 EULAR recommendations for the management of gout[6] are very similar to recommendations in other current evidence-based, expert consensus guidelines from international rheumatology societies.[65,92,93] A few differences in the 2012 ACR guidelines,[65,92] which are discussed elsewhere in greater detail,[94] include: 1) the recommendation to consider commencement of ULT during the course of a gout flare; 2) the use of low-dose corticosteroids (prednisolone <10 mg/d) for flare prophylaxis if colchicine and NSAIDs are contraindicated; 3) the use of febuxostat as well as allopurinol for first-line ULT; 4) careful uptitration of allopurinol in patients with impairment of renal function; and 5) screening Koreans with CKD stage 3 or worse and all patients of Han Chinese and Thai descent for HLA-B*5801 before considering ULT with allopurinol,[65] because of a greatly increased risk of allopurinol-induced SCARs in subjects carrying this variant allele and a high allele frequency (6%–12%) in these ethnic groups.[95] Screening for HLA-B*5801 is not currently recommended in Europe where the risk of developing allopurinol-induced SCARs in HLA-B*5801-positive individuals is lower[96,97] and the allele frequency in Caucasians is lower (1%–2%).

Conclusions Surprisingly, the recommendation to eliminate urate crystals through lifelong lowering of SU below a target level, which is one of the overarching EULAR principles, and a key recommendation in all guidelines for the management of gout from international rheumatology societies,[6,65,92,93] has recently been challenged in a clinical practice guideline from the American College of Physicians (ACP).[98] Based on a systematic evidence review sponsored by the AHRQ and conducted by the RAND Corporation's Southern California Evidence-based Practice Center, the ACP concluded that it was inappropriate to recommend a treat-to-target strategy as this was not supported by RCT evidence of clinical benefit, such as reduction in the frequency of gout flares, but mainly by retrospective studies and studies that used SU as the primary outcome measure. The ACP guideline recommends "treatment to avoid symptoms" without monitoring SU levels. There is, however, no evidence to support the efficacy or safety of such an approach, which is similar to the current standard of care for patients with gout in general practice,[2,3,9] and which has notably failed to prevent the rising prevalence of gout.[7] By contrast, a nurse-led treatment-to--target approach following the EULAR recommendations resulted in a reduction of SU levels to target in more than 90% of patients and improvements in patient-centered outcomes and quality of life, when compared with general practitioner--led usual care, in a 2-year community-based comparative effectiveness RCT in over 500 patients with gout in the United Kingdom.[99]

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