

Italian Society of Rheumatology recommendations for the management of gout

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SUMMARY

Objective: Gout is the most common arthritis in adults. Despite the availability of valid therapeutic options, the management of patients with gout is still suboptimal. The Italian Society of Rheumatology (SIR) aimed to update, adapt to national context and disseminate the 2006 EULAR recommendations for the management of gout.

Methods: The multidisciplinary group of experts included rheumatologists, general practitioners, internists, geriatricians, nephrologists, cardiologists and evidence-based medicine experts. To maintain consistency with EULAR recommendations, a similar methodology was utilized by the Italian group. The original propositions were translated in Italian and priority research queries were identified through a Delphi consensus approach. A systematic search was conducted for selected queries. Efficacy and safety data on drugs reported in RCTs were combined in a meta-analysis where feasible. The strength of recommendation was measured by utilising the EULAR ordinal and visual analogue scales.

Results: The original 12 propositions were translated and adapted to Italian context. Further evidences were collected about the role of diet in the non-pharmacological treatment of gout and the efficacy of oral corticosteroids and low-dose colchicine in the management of acute attacks. Statements concerning uricosuric treatments were withdrawn and replaced with a proposition focused on a new urate lowering agent, febuxostat. A research agenda was developed to identify topics still not adequately investigated concerning the management of gout.

Conclusions: The SIR has developed updated recommendations for the management of gout adapted to the Italian healthcare system. Their implementation in clinical practice is expected to improve the management of patients with gout.

Key words: Gout, treatment, recommendations.

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■ INTRODUCTION

Gout is the most common arthritis in adults with a prevalence of between 0.9% in Italy and 3.9% in the USA and with an increasing incidence in Italy and other developed countries (1, 2). Apart from its high frequency, gout is associated with disability, lower quality of life and increased mortality and therefore represents an ever-increasing public health concern (3-5).

Despite the current in-depth knowledge and the availability of valid therapeutic options in gout, the management of patients with gout is still largely suboptimal (6). A fundamental prerequisite of gout is hyperuricaemia which is defined as the presence of serum uric acid levels above 6.8 mg/dL (404 $\mu\text{mol/L}$) which approximately mark the saturation point of monosodium urate (MSU) at physiological temperature and pH (7). The pathophysiological model portrays, in the presence of hyperuricaemia, the intra-articular deposition of MSU crystals which is responsible for the onset of an acute attack and chronic arthropathy. The management of patients with gout is based on this simplified model and thus implies the control of risk factors related to hyperuricaemia, the effective and rapid control of acute attacks and the persistent reduction of serum MSU levels.

These 3 intervention levels represent the basic principles of the 2006 EULAR recommendations on the management of gout compiled by a task force of European experts (8). The Italian Society of Rheumatology (SIR) has deemed imperative the adaptation, updating and dissemination of the EULAR recommendations for gout.

This document is intended for rheumatologists, general practitioners, internists, geriatricians, nephrologists, cardiologists and all healthcare professionals involved in the management of patients with gout.

■ MATERIALS AND METHODS

A multidisciplinary group of experts has been appointed by the SIR in order to up-

date and adapt to Italian context the 2006 EULAR recommendations on the management of patients with gout (8). The group of experts who have accepted to participate included rheumatologists and specialists from various scientific societies involved in the diagnosis and treatment of patients affected by gout such as nephrology, internal medicine, geriatrics, cardiology and general medicine.

The objectives of the task force were the following: translation of the recommendations, adaptation to the Italian pharmaceutical formulary (taking in consideration the available drugs and new therapeutic options), identification of priority queries for further analysis, collection of evidence and its critical interpretation, definition of propositions based on the merger of the best available evidence and expert opinion.

The expert panel was subdivided in 3 multidisciplinary groups which respectively worked upon 3 levels of intervention: comorbidities and lifestyle; acute attack management; management of chronic gout. The original propositions have been translated by each of the multidisciplinary groups and subsequently approved by the whole panel.

The identification of the research queries has been conducted through the Delphi technique. In order to classify the items under the 3 levels (comorbidities and lifestyle; acute attack management; long-term management of gout), separate voting for each item has been conducted and the 4 top ranking queries were selected. These 4 queries, which were subsequently rephrased according to the PICO (*Population-Intervention-Comparator-Outcome*) strategy, where:

1. does the consumption of specific foods and beverages influence the disease outcome (e.g. uricaemia, number of flares, disability, mortality) in patients with gout?;
2. is the administration of oral corticosteroids, with respect to other forms of treatment, effective and safe in patients with an acute attack of gout?;
3. is low-dose colchicine (0.5 mg up to 3 time daily), with respect to higher dose

- administration, effective and safe in patients with an acute attack of gout?;
4. is febuxostat, with respect to other forms of urate lowering treatment or no treatment at all, effective and safe in patients with chronic gout?

A systematic search strategy has been defined for each query. The 4 searches have been undertaken on the main electronic bibliographic databases (Medline, Embase and Cochrane Library), in the timeframe between 1/1/1950 and 25/3/2012 and restricting the search to publications in Italian and English and to studies on human beings. Moreover, the search has been enhanced with a manual search in the proceedings of the 2010 and 2011 EULAR and ACR congresses, and in the reference lists of the studies included from the electronic search.

Inclusion criteria have been defined for each query, and subsequently, an *ad hoc* extraction form has been developed. The article selection for each query has been conducted by a single reviewer (MM, AB, MF and IP). Only studies regarding the clinical aspects of gout were included. Studies on hyperuricaemia were only included when an evaluation of the influence of specific factors (*e.g.* eating habits) on the onset on gout was conducted. Studies with the following design were included: systematic review and meta-analysis, randomised control trial (RCT) and controlled study for efficacy and safety queries, and also cohort studies, case control and cross-sectional studies for risk factor queries. Case reports, narrative reviews and editorials were excluded in all cases.

Efficacy and safety data on drugs reported in RCTs have been combined in a meta-analysis where feasible, and presented as standardized mean differences [SMD or effect size (ES)], Number Needed to Treat (NNT) or risk ratio (RR), and relative Confidence Intervals (CI) at 95%. From the clinical perspective, an ES of 0.20 is considered low, 0.5 as moderate and more than 0.80 as high. The NNT is the number of patients who have to be treated in order to obtain the desired effect (or prevent an unwanted effect) in one of them, and there-

Table I - Level of evidence.

Ia	Meta-analysis of randomised control trials
Ib	Randomised control trial
IIa	Controlled study without randomisation
IIb	Quasi-experimental study
III	Non-experimental descriptive studies
IV	Expert committee reports or opinion or clinical experience of respected authorities, or both

fore a lower value corresponds to higher efficacy. On the basis of the study design, the impact of risk factors has been expressed as RR or odds ratio (OR). The ES calculations and the resulting meta-analyses have been created with Review Manager (Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011).

The level of evidence for efficacy has been assigned according to the design of the included studies via a preestablished hierarchy (Tab. I). The search results therefore consisted of the highest level of evidence available: for example, if a systematic review of RCTs was available, the existing literature review was updated and studies with a weaker design were excluded. Queries on risk factors or adverse effects were based on both RCTs and observational studies. Studies with direct evidence were first considered, and indirect evidence studies were only analysed when direct evidence studies were unavailable.

In order to maintain consistency with Eular recommendations, the strength of recommendation (SOR) was measured for each proposition by utilising the EULAR A-E ordinal scale (A=fully recommended; B=strongly recommended; C=moderately recommended; D=weakly recommended; E=not recommended) and a 0-100 mm visual analogue scale (VAS) (8), by taking into consideration both the evidence (efficacy, safety and cost-effectiveness) and the clinical experience (feasibility, acceptability and tolerance). The results of each proposition were reported as mean of the VAS with 95% CI and as percentage of fully or strongly recommended propositions (A-B).

■ RESULTS

Optimal treatment of gout requires both non-pharmacological and pharmacological modalities and should be tailored according to:

- 1. specific risk factors (levels of serum urate, previous attacks, changes in imaging);**
- 2. clinical phase (acute/recurrent gout, intercritical gout, and chronic tophaceous gout);**
- 3. general risk factors (age, sex, obesity, alcohol consumption, urate elevating drugs, drug interactions and comorbidity).**

Strength of recommendation (95% CI): 86 (79, 93)

Comments. The original proposition was acknowledged by the Italian expert panel. The only alteration was 'radiographic signs' to the more inclusive 'changes in imaging'. By doing so the experts aimed to highlight the importance, apart that of 'traditional' radiology, of recently introduced imaging technologies such as ultrasound and magnetic resonance despite that their usefulness in the management of the patient with gout is still unproven.

The 2006 EULAR recommendations highlighted that the management strategy of the patient with gout varies according to the clinical presentation (hyperuricaemia alone, acute gout or chronic tophaceous gout in the intercritical phase). Patient advice and dosage depend on various factors such as comorbidities, risk factors (overweight and alcohol consumption), age, sex and demographics. A cohort study comparing the long-term effects of urate lowering treatment in patients with chronic gout with different clinical patterns (absence or presence of tophi and radiological damage) has not shown significant between-group differences (9). However, non-controlled studies have shown that the dose of allopurinol needed to reach the target serum uric acid level can vary among different patient subgroups (10, 11) while two RCTs have shown the influence of comorbidities, such as hypertension and renal insufficiency, on

treatment response (12, 13). The efficacy of pharmacological and non-pharmacological treatment is well documented in the long-term management of patients with chronic gout (14-16) and their complementarity seems rational even through the results of a study which has demonstrated that a combination of topical ice application and colchicine administration enhances the anti-inflammatory and analgesic effects of monotherapy (17). The use of non-pharmacological treatment, with consideration of the minor adverse events risk and costs, is advised in all cases of long-term patient care. Caution is to be exercised in pharmacological treatment to avoid adverse interaction effects of allopurinol with other drugs, such as erythromycin and cyclosporine (18, 19).

Conclusions. The clinical phase (*level Ib*), uricaemia and frequency of previous acute attacks (*level IIb*), risk factors and associated comorbidities (*level Ib*) are to be taken in consideration in the management of the patient with gout. There is evidence showing that the combination of pharmacological and non-pharmacological treatment is more effective than monotherapy (*level Ib*).

Patient education and appropriate lifestyle advice (healthy diet and reduced consumption of beverages containing fructose and alcohol, beer especially) are core aspects of management.

Strength of recommendation (95% CI): 83 (75, 91)

Comments. The proposition has been partially modified by the Italian expert panel. The statement 'weight loss if obese' was omitted since it was deemed that management of this comorbidity would be better assessed in proposition number 3. The impact of food and beverage consumption on the risk of developing gout has been reevaluated through the updating of the 2006 EULAR recommendations literature review.

The 2006 EULAR recommendations have identified patient education as an important element of the management of gout, especially education on lifestyle change and compliance to long-term urate lowering

therapy. However, in absence of specific studies on the issue, the recommendation was based on expert opinion alone.

Two prospective cohort studies have shown that purine-rich food, such as meat and seafood, are associated with an increased risk of gout. The first study showed a RR of 1.21 (95% CI: 1.04, 1.41) for meat consumption and 1.07 (1.02, 1.12) for seafood consumption (20); the second study reported a RR of 1.45 (1.06, 1.92) for meat consumption (21).

Various studies have shown that alcohol consumption is associated with a higher risk of developing gout which incrementally increases in relation to the amount of alcohol consumed (21-32). A prospective cohort study has shown that the risk of developing gout varies among different types of alcohol consumed: daily consumption of beer was associated with a RR of 1.49 (1.32, 1.70), spirits posed a RR of 1.15 (1.04, 1.28) while wine, at the studied consumption levels (approx. 120 mL daily), did not result in a significant increased risk of gout development (25). Moreover, beer might exert an alcohol-independent effect on gout risk due to its high purine content. More recently, an association between fructose-containing beverages and onset of gout has been demonstrated in a prospective study on a large cohort of men where daily consumption of sweetened beverages was associated with a RR of 1.45 (1.02, 2.08) of developing gout (33), while another study on women showed a RR of 1.74 (1.19, 2.25) for daily consumption with respect to consumption of sweetened beverages equal to or less than once a month (34). Moreover, analysis of the overall fructose intake among the same cohorts showed an increased RR of developing gout in the upper quintile compared with the lower one in both men 2.02 (1.49, 2.75) and women 1.43 (1.09, 1.88) (33, 34).

There is conflicting evidence on the risk of gout associated with fruit consumption: the aforementioned study has shown that consumption of at least one fruit a day is associated with a RR of 1.64 (1.05, 2.56) of developing gout (33) while another prospective study shows a reduction of RR

[0.73 (0.62, 0.84)] in subjects with a higher consumption of fruit.

Dairy products, especially low-fat products, seem to exhibit a protective role in gout: their consumption has been associated with a reduction in risk of developing gout in a large cohort of healthy participants [RR 0.79 (0.71, 0.87)]. A RCT has shown a significant reduction in the number of flares in patients with gout who consumed skimmed milk enriched with certain compounds (glycomacropeptide and lipid extract G600) when compared to a control (lactose), suggesting that these compounds could explain the protective effect of dairy products in individuals with gout (35). The long-term consumption of coffee in the general population has been associated with a decreased incidence of gout (36, 37). Recent studies have suggested vitamin C as a protective dietary compound (29, 38).

Conclusions. There is widespread consensus on the importance of patient education in improving outcome by affecting compliance and lifestyle change (*level IV*). There is evidence in the general population that consumption of purine-rich foods and beverages containing alcohol and fructose is a risk factor for gout, while consumption of milk, low-fat dairy products, coffee and vitamin C is reported as having a protective effect on gout (*level III*). Therefore, despite the absence of studies directly assessing the role of diet modification on disease-related outcomes in patients with gout, dietary intervention should be considered in the management of gout (*level IV*).

Associated comorbidity and risk factors such as hyperlipidaemia, hypertension, hyperglycaemia, obesity and smoking should be addressed as an important part of the management of gout.

Strength of recommendation (95% CI): 85 (78, 93)

Comments. This proposition was only translated since the expert panel voted unanimously in favour of this proposition and did not deem any modification necessary. The association between hyperuricae-

mia and the 'metabolic syndrome' (hyperlipidaemia (39-41), hypertension (42, 43), diabetes and insulin resistance (44, 45) and obesity) is well reported. It is therefore good clinical practice to address these clinical conditions in the management of a patient with gout. Although there is no direct evidence of the role of tobacco smoking as a risk factor for gout, smoking has shown a strong association with alcohol consumption (46) which is in turn associated with a significant increment in the risk of gout. Moreover, smoking is a modifiable risk factor for cardiovascular disease and is to be therefore addressed in a holistic model of patient care.

Evidence from RCTs has also shown that some drugs used for the treatment of such comorbidities, such as fenofibrates and losartan, have a concomitant urate lowering effect (47-52).

Conclusions. The identification and treatment of comorbidities are to be considered as an essential part of the management of gout since such approach can offer benefits in the treatment of both comorbidities and gout itself (level Ib).

Oral colchicine and/or NSAIDs, including COX-2 inhibitors, are first line agents for systemic treatment of acute gout. Corticosteroids are a convenient and well accepted option. However, comorbidities and contraindications are to be taken into account in the choice of treatment.

Strength of recommendation (95% CI):
93 (90, 97)

Comments. The management of an acute attack of gout is based on the use of NSAIDs, oral colchicine or corticosteroids, preferably in the first 12-24 hours from the onset of symptoms. The 2006 EULAR recommendations, which were based on RCT analysis, have concluded that colchicine and NSAIDs are of comparable efficacy. The superior clinical efficacy of colchicine with respect to a placebo in the reduction of pain severity during an acute attack of gout and the lower incidence of adverse gastrointestinal effects (mainly

vomiting and diarrhoea) with low-dose colchicine with respect to higher doses have been demonstrated in two RCTs (16,53). NSAIDs show comparable efficacy to that of colchicine regardless of their different mechanism of action and lack of NSAID-colchicine 'head to head' comparative studies. A RCT has shown higher efficacy with tenoxicam than with a placebo in the resolution of an acute attack of gout (54). Various comparative studies have shown similar efficacy among different NSAIDs. Their safety profile, particularly the risk of gastrointestinal complications, is to be taken into account. Evidence from a meta-analysis suggests the concomitant use of gastroprotective drugs or opting for COX-2 inhibitors as precautions to minimise adverse effects and cautious monitoring in patients with cardiovascular comorbidities when COX-2 inhibitors are opted for (8).

Corticosteroid use is an alternative to consider in selected cases. Five RCTs on the efficacy of systemic corticosteroids (oral formulations or parenteral triamcinolone acetate) have been collectively analysed in the systematic literature review (55-59). The study by Janssens et al. (58) on 118 patients has shown that a 5-day administration of oral prednisolone is of comparable efficacy with that of naproxen in pain relief at 90 hours [ES (95% CI): -0.06 (-0.42, 0.31)] and in increasing function [ES: 0.01 (-0.37, 0.35)]; similarly the study by Man et al. (57) has shown the equivalent efficacy of 5-day administration of prednisolone with that of indometacin in pain relief during the first two hours [ES: 0.33 (-0.09, 0.74)] and a higher efficacy of prednisolone at 2 weeks [ES: 0.70 (0.25, 1.14)]. A more recent study on 200 patients has compared the efficacy of triamcinolone with that of a recombinant anti-IL1 monoclonal antibody (59). Triamcinolone has shown slightly lower efficacy in pain relief on a visual analogue scale (VAS) at 72 h [ES: -0.42 (-0.73, -0.10)] and at one week [ES: -0.33 (-0.64, -0.02)]. Overall, with regards to safety, there were no reported differences in the number of adverse events in between patients treated with corticosteroids and those treated with another drug

(NSAIDs, canakinumab) although adverse drug events for short-term treatment were lower in patients on corticosteroids [RR: 0.53 (0.23, 1.19)].

Conclusions. In conclusion, oral colchicine, NSAIDs (non-selective and specific COX-2 inhibitors) and corticosteroids are effective in relieving the symptoms of an acute attack of gout (level Ib). High-dose colchicine can cause diarrhoea while non-selective NSAIDs are associated with a higher risk of gastrointestinal adverse events. Corticosteroids are an effective and safe alternative in cases of intolerance or contraindications to both colchicine and NSAIDs.

Low-dose colchicine (up to 2 mg daily) is effective and safe for some patients with acute gout.

Strength of recommendation (95% CI): 86 (81, 91)

Comments. The efficacy of treatment of acute gout with colchicine has been shown by 2 RCTs (16,53). The 1987 study by Ahern et al. (16) compared treatment efficacy with colchicine (1 mg followed by 0.5 mg every 2 hours up to full therapeutic response or toxicity) to placebo while the 2010 study of Terkeltaub et al. (53) compared low (up to 1.8 mg) and high doses (up to 4.8 mg) of colchicine between themselves and separately with a placebo. Ahern et al. (16) have shown the superior efficacy of colchicine to placebo in relieving pain in an acute attack of gout (73% of patients on colchicine vs 32% of patients on a placebo at 36 h; 73% of patients on colchicine vs 36% of patients on a placebo at 48 h). The study of Terkeltaub et al. (53) has also shown the higher efficacy of colchicine at both low doses [OR (95% CI) of 3.31 (1.41,7.77)] and high doses [OR (95% CI) of 2.64 (1.06, 6.62)] when compared to placebo, for the relief of 50% of pain at 24 h. Both studies demonstrated a higher risk of side effects (from 76.9% to 100%) for high-doses colchicine, with an OR of 9.0 (3.8, 21.2) when compared to placebo. Moreover, colchicine at low doses was safer than at high doses and it showed a safety

profile similar to placebo, with an OR for adverse events of 1.5 (0.7, 3.2) (60).

The 2010 RCT has added scientific evidence to the 2006 EULAR literature review which until then supported this proposition with expert opinion alone, that is the recommendation that low-dose colchicine is equally effective as high-dose administration and with the added benefit of a lower incidence of adverse effects. The following NNTs for the relief of 50% of pain were observed when combining data from both studies with a meta-analysis: 4.34 (2.77, 11.11) for high-dose colchicine vs placebo, 4.54 (2.70, 12.50) for low-dose colchicine vs placebo and 20 (4.45, ∞) for low-dose vs high-dose colchicine. The combined data on safety have identified a higher risk of gastrointestinal adverse effects for high-dose colchicine vs placebo [RR: 43.04 (2.78, 667.15)], and also a significantly lower RR for low vs high dosage [0.33 (0.22, 0.51)] of colchicine. Low-dose colchicine has been defined as up to 2 mg daily since the 1mg formulation is the only one available in the Italian formulary.

Conclusions. Both low-dose and high-dose colchicine are effective in the treatment of an acute attack of gout when compared to placebo (level Ib). Low-dose colchicine is safer than high-dose administration in the treatment of acute attacks (level Ib).

Intra-articular aspiration and injection of a long acting steroid is an effective and safe treatment for an acute attack.

Strength of recommendation (95% CI): 86 (78, 94)

Comments. The original proposition was not changed. The experts deemed relevant to highlight the importance to exclude the presence, concomitant or alone, of infective arthritis before a corticosteroid infiltration is undertaken. The 2006 EULAR recommendations data have shown that there are no controlled clinical studies in support of the efficacy and safety of arthrocentesis and joint infiltration despite that both are commonly performed procedures. The EULAR review reported only one non-controlled study on 19 patients in which a

single dose of 10 mg triamcinolone acetonide was given intra-articularly resulting in pain relief without side effects (61).

Conclusion. A sustained-release corticosteroid infiltration is effective for pain relief in an acute attack (level IIb).

Urate lowering therapy is indicated in patients with recurrent acute attacks, chronic arthropathy, tophi, or changes in imaging typical of gout.

Strength of recommendation (95% CI): 9I (87, 95)

Comments. The pathophysiological model of gout considers the tissue deposition of MSU crystals as the cause of both acute attacks and chronic disease. The treatment objective is therefore to reduce serum uric acid levels below saturation point and to remove MSU deposits. Lifestyle interventions, especially dietary ones, are often not enough to reach this goal and hence the use of urate lowering treatment is resorted to. There are no scientific data which show when best to start treatment. Experts suggest to start urate lowering treatment in patients with recurrent acute attacks, gout arthropathy, characteristic changes in imaging or presence of tophi. Italian experts highlight that any decision on when to start treatment is to be tailor-made to the needs of the patients and the risk-benefit ratio of the chosen treatment (proposition 1).

Conclusions. In conclusion, the experts support the indication of urate lowering treatment in patients with recurrent acute attacks, arthropathy, tophi, or characteristic changes in imaging (level IV).

The therapeutic goal of urate lowering therapy is to promote crystal dissolution and prevent monosodium urate crystal formation. This is achieved by maintaining the serum uric acid below the saturation point for monosodium urate (≤ 360 $\mu\text{mol/L}$ or ≤ 6 mg/dL).

Strength of recommendation (95% CI): 9I (87, 95)

Comments. Gout is a MSU crystallopathy. The mechanism of tissue deposition de-

pends on local articular conditions and intra-articular uric acid concentrations, hence the reason why not all individuals with hyperuricaemia develop gout. Gout management aims to maintain intra-articular uric acid levels below its saturation point in order to prevent the formation of new deposits and to allow the dissolution of those already formed. Serum uric acid levels are a good indicator of intra-articular levels and thence are a good therapeutic indicator and biomarker for the intra-articular pathological status. A serum uric acid level of ≤ 6 mg/dL reflects tissue levels which are probably below saturation point. Various studies have shown the benefits and advantages of these serum uric acid levels (62, 63).

A retrospective study on 5942 patients and an analysis of administration databases of 18,243 patients with gout have shown that serum urate levels of >6 mg/dL are associated with a significant increase in risk of an acute attack with an OR of 1.59 (95% CI: 1.21, 2.09) and 1.29 (1.07, 1.56), respectively (64,65). Another observational study on 2237 patients of over 65 years of age has shown an increase in the risk of an acute attack of 12% for each unit of increment in serum uric acid levels above 6 mg/dL (66). Lowering of uric acid levels has been also associated with a decrease in the size of tophi (62); such evidence has supported targets of serum uric acid levels below 4 mg/dL as short-term goal in the aggressive treatment of tophaceous gout (63).

Conclusions. The aim of urate lowering treatment is to promote the dissolution and to prevent the formation of tissue MSU crystals deposits. Serum uric acid levels are to be maintained below 6 mg/dL , a level which reflects tissue concentrations below MSU saturation point (level III).

Allopurinol is an appropriate long-term urate lowering therapy. It should be started at a low dose (100 mg daily) and increased by 100 mg every two to four weeks if required. The dose must be adjusted in patients with renal impairment. If allopurinol toxicity occurs, options include uricosuric agents (when available) or other xanthine oxidase inhibitors.

Strength of recommendation (95% CI): 88 (82, 94)

Comments. Although allopurinol is the most commonly administered urate lowering drug in the long-term treatment of gout, the first RCT showing its efficacy by comparison with a placebo and febuxostat has been only conducted in 2008 (67). In this trial, a dose of 300 mg of allopurinol has been associated with an ES of 2.34 (95% CI: 2.07, 2.60) on lowering serum uric acid levels and a NNT of 2.63 (2.27, 3.12) to reach therapeutic serum uric acid levels.

Results from non-controlled studies reported in the EULAR recommendations (10, 11) have shown a dose-dependent response to allopurinol of a lowering of 1 mg of serum uric acid levels for every 100 mg of allopurinol increase.

These results support the need of slow titration of the allopurinol dose till the attainment of target levels. A 'dose-escalation' study has shown that a daily dose increment of 300 to 600 mg is associated with serum uric acid levels of <5.5 mg/dL in 78% of patients (68, 69).

Allopurinol can cause potentially serious adverse reactions such as the hypersensitivity syndrome characterised by cutaneous desquamation, fever, hepatitis, eosinophilia, renal failure and a mortality rate of up to 20% (68, 70). Despite its potential benefit in mild hypersensitivity reactions, desensitisation is not recommended since it is deemed as an obsolete and potentially harmful procedure.

Allopurinol is mainly excreted in urine and its mebatolite, oxypurinol, can accumulate to toxic levels in patients with renal insufficiency, therefore, lower starting doses (50-100 mg) are indicated in this group of patients (71).

A low-dose start of allopurinol and gradual increments at 2-4 weeks are recommended in light of efficacy and safety data. Despite lack of supporting experimental data, this regimen reduces the frequency of acute attacks on starting treatment, reduces the incidence of adverse reactions and identifies the patient-specific minimum effective dose required to maintain optimal serum uric acid levels.

Table II - Urate lowering drugs in the Italian formulary.

Active ingredient	Dosage
Allopurinol 100 mg 300 mg	100-300 mg, up to 800 mg daily spread on 2-3 doses. According to Creatine clearance: Cr>20mL/min: 300 mg daily Cr of 10-20 mL/min: 100-200 mg daily ClCr<10 mL/min: 100 mg daily or at longer intervals
Febuxostat 80 mg 120 mg	80-120 mg
Sulphinpyrazone (off label) 400 mg	400 mg daily, up to 800 mg

Probenecid and benzbromarone, alternative therapeutic options recommended by the 2006 EULAR recommendations, are not available in the Italian formulary. Although no data on the efficacy with sulphinyprazole in patients with gout are available, its off label administration is a treatment option as monotherapy for patients in which other urate lowering agents are contraindicated or as a combination drug with a xanthine oxidase inhibitor in treatment-resistant cases (Tab. II).

Conclusions. In conclusion, allopurinol is effective as long-term treatment of chronic gout (*level Ib*) via a dose-dependent urate lowering effect (*level Iib*).

Despite the lack of experimental data, a daily starting dose of 100 mg with successive increments to doses reaching the therapeutic goal is preferable to a fixed dosage, especially in patients with renal insufficiency (*level IV*). Alternative urate lowering agents can be considered in certain cases such as allopurinol hypersensitivity (*level IV*).

Febuxostat is an effective alternative to allopurinol which shows greater efficacy and minor adverse effects as urate lowering agent. Starting doses are to be low and increased if necessary.

Strength of recommendation (95% CI): 82 (76, 89)

Comments. Febuxostat was only recently introduced in Italy as an alternative to allopurinol. Febuxostat is a non-purine urate lowering agent whose mechanism of action is selective inhibition of xanthine oxidase. Febuxostat efficacy and safety data have been mainly collected through an *ad hoc* systematic review and RCT meta-analysis which compared febuxostat at any dose to allopurinol. The analysed efficacy outcomes were relative to therapeutic target (*disease-oriented*) and flareup risk (*patient-oriented*) while safety outcomes related to serious adverse events.

A 52-week double blind RCT on 760 patients on either 80 mg or 120 mg febuxostat, or 300 mg allopurinol has shown that a significantly larger number of patients on febuxostat, when compared with patients on allopurinol, had serum uric acid levels of ≤ 6.0 mg/dL (72) with a NNT of 4 (95% CI: 3.3, 5) with the 80 mg dose and 2.2 (1.8, 2.6) with a dose of 120 mg at the last followup session. A parallel increase in the risk of acute attacks in the groups of patients on 120 mg febuxostat was not statistically significant. A phase III RCT on 1072 patients with gout, uricaemia of ≥ 8.0 mg/dL and a subgroup of patients with moderate renal insufficiency compared the efficacy and safety of 80 mg, 120 mg and 240 mg of febuxostat with those of 300 mg of allopurinol. Patients with renal insufficiency (plasma creatine levels of 1.5-2.0 mg/dL) were administered fixed doses of 80 mg, 120 mg and 240 mg of febuxostat or low-

dose (100 mg) allopurinol. A significantly larger proportion of patients on febuxostat reached the primary endpoint defined as levels of serum uric acid of ≤ 6.0 mg/dL sustained on the last 3 followup sessions [NNT (95%CI): 2.22 (1.81, 2.63)]. Efficacy proportionally increased with dose (NNT 2.85, 2.17 and 1.88 for febuxostat 80 mg, 120 mg and 240 mg, respectively). A statistically significant dose-dependent flareup risk was also reported when comparing 240 mg febuxostat to allopurinol (67).

A 6-month RCT has compared the efficacy and safety of 40 mg and 80 mg of febuxostat to 300/200 mg of allopurinol in a stratified sample of 2269 patients with gout and serum uric acid level of ≥ 8 mg/dL, and with at least 35% of participants with low or moderate renal insufficiency (73). While the number of participants with serum uric acid levels of ≤ 6.0 mg/dL at the end of the study did not significantly differ between the 40 mg of febuxostat and 300 mg of allopurinol groups [NNT: 33.33 (12.50, ∞)], a significantly difference in number was shown in the 80 mg febuxostat group [NNT: 4.00 (3.33, 5.00)]. No flareup risk analysis was reported in the study.

Moreover, 2 small RCTs were identified by the systematic literature search and included in 2 meta-analyses which focused on two prespecified outcomes: achieving therapeutic target of urate and risk of acute attacks (74, 75).

Data from the first meta-analysis has shown a greater likelihood to reach the therapeutic target with febuxostat at 80 mg or more than with 300 mg of allopurinol (Tab. III).

Table III - RCT meta-analysis comparing efficacy and safety of febuxostat and allopurinol in patients with gout.

Outcome	Association measure	Febuxostat			
		40 mg	80 mg	120 mg	240 mg
Target <6 mg/dL	NNT (95% CI)	20 (11.1, ∞)*	3.2 (2.9, 3.6)*	2.3 (2.1, 2.6)*	1.9 (1.6, 2.2)*
Flareup	RR (95% CI)	-	1.06 (0.93, 1.21)*	1.29 (0.87, 1.91) ^o	2.26 (1.72, 2.98)*
Serious adverse events	RR (95% CI)	0.65 (0.41, 1.03)*	0.74 (0.51, 1.06)*	1.11 (0.61, 2.02)*	-

*Fixed model; ^orandom effect model. NNT, number needed to treat; RR, risk ratio; CI, confidence interval.

The second meta-analysis has shown a higher risk of an acute attack onset with high-dose febuxostat than with allopurinol although this difference was not statistically different at the commonly prescribed febuxostat dosages of 80 mg and 120 mg. The combined safety data analysis comparing febuxostat and allopurinol has not shown statistically significant difference between 300 mg allopurinol and febuxostat at any single dose, however the combined RR for all combined doses skews slightly in favour of febuxostat [RR: 0.76 (0.59, 0.98)].

In interpreting the above results it is important to consider the inclusion of participants with previous failure with allopurinol treatment and the fixed dose of allopurinol at 300 mg.

Additional data from observational studies and from a subanalysis and an observational extension of RCTs has provided further information on the efficacy and safety of febuxostat.

An open label extension of a phase II RCT has evaluated the efficacy and safety of febuxostat at 5 years in 116 patients and has shown a lowering of serum uric acid levels to ≤ 6 mg/dL in 83% of participants and resolution of tophi in 69% at the last follow-up session with none of the participants experiencing adverse drug reactions.

The RCT extension study has compared the safety of 80 mg and 120 mg of febuxostat to 300 mg of allopurinol on a cohort of 1086 patients with gout and hyperuricaemia. Comparative results have shown the superior efficacy of 80 mg of febuxostat on 300 mg of allopurinol [RR 1.76 (1.46, 2.11)] in reaching therapeutic target at 6 months, although such difference in efficacy decreased thereafter; the same study has shown a long-term reduction in the dimensions of tophi and progressive flareup risk reduction with all treatment regimes (76).

A retrospective study on 13 patients has shown a good security profile on individuals with past severe adverse reactions to allopurinol (77).

An increase in the risk of adverse cardiovascular events has not yet been supported by RCT data (78).

Conclusions. Febuxostat is an effective urate lowering agent (*level Ia*) in patients with gout and has shown greater efficacy at a dosage of 80 mg or more when compared to allopurinol at the maximum dose of 300 mg in the short-term control of hyperuricaemia (*level Ia*). Treatment with febuxostat has been shown to be safer in patients with mild or moderate renal insufficiency when compared to treatment with allopurinol (*level Ib*).

Prophylaxis against acute attack during the first months of urate lowering therapy can be achieved with colchicine (0.5 mg to 1mg daily) and/or NSAIDs. If not contraindicated, low-dose corticosteroids are a feasible alternative in refractory cases or cases of drug intolerance.

Strength of recommendation (95% CI): 87 (81, 93)

Comments. The start of urate lowering therapy can precipitate an acute attack of gout in response to a rapid drug-induced reduction of serum uric acid levels. Therefore, prophylactic treatment is an integral part of appropriate management. The 2006 EULAR recommendations highlighted the administration of oral colchicine and/or NSAIDs as first line prophylactic treatment for acute attacks. Two controlled clinical studies have evaluated and shown the prophylactic efficacy of colchicine (79, 80). A controlled study on patients with gout who have started treatment with allopurinol has compared the efficacy of colchicine (0.6 mg daily) to a placebo and has shown a significant reduction in the number of acute attacks [7/21 vs 17/22, NNT 2 (1-6)] but an increase in adverse gastrointestinal effects (diarrhoea) [RR (95% CI): 8.38 (1.14, 61.38)] during the first three months of therapy with colchicine combined with allopurinol. Another study on 52 patients with intercritical phase gout has compared the efficacy of combined probenecid (500 mg three times daily) and low-dose colchicine (0.5 mg daily) to probenecid monotherapy. Similar efficacy in serum uric acid reduction and safety has been reported for both regimens although a significantly lower number of acute attacks

was observed in the combination treatment group [ES: 0.74 (0.08, 1.4)].

NSAIDs can also be administered prophylactically for the prevention of acute attack onset in the first few months of urate lowering treatment. In this regard, two RCTs have shown in patients on allopurinol a prophylactic effect from acute attacks of a dose of 600 mg twice daily of azapropazone, a uricosuric NSAID (81); conversely, an increase in the number of adverse gastrointestinal events was reported in the combination therapy group. Evidence on the adequate duration of prophylactic treatment is variable. A risk-benefit balance is required when starting prophylactic NSAID treatment in which gastrointestinal intolerance and renal insufficiency, as well as cardiovascular and renal toxicity in prolonged treatment are to be taken into account. In such cases, 3 to 6-month corticosteroid administration could be a valid alternative. However, there is no direct evidence on corticosteroid efficacy and no studies which have evaluated their long-term prophylactic efficacy and safety in patients starting urate lowering treatment.

Conclusions. Strong evidence supports the prophylactic administration of oral colchicine for the prevention of acute gout remissions in the first few months of urate lowering treatment (*level Ib*), while data on NSAID administration is as yet inconclusive (*level Iia*). Efficacy with low-dose corticosteroids has not been proven with direct evidence and therefore their use is supported by expert opinion alone (*level IV*).

When gout associates with diuretic therapy, stop the diuretic if possible. For hypertension and hyperlipidaemia consider the use of losartan and fenofibrate, respectively (both have modest uricosuric effects).

Strength of recommendation (95% CI): 87 (82, 92)

Comments. This proposition was only translated since the expert panel voted unanimously in favour of this proposition and did not deem any modification to be necessary.

Diuretics, which are widely prescribed among the general population, are a main risk factor of gout [OR (95% CI): 1.72 (1.67, 1.76)] (82). Depending on its indication in patients who developed gout, diuretic therapy can either be stopped or changed with a suitable alternative. Non-thiazide diuretics are to be prescribed to patients with concomitant gout and hypertension. Losartan, an angiotensin II receptor antagonist manifesting uricosuric properties, can therefore reduce both blood pressure and serum uric acid levels (50-52).

Apart from hypertension, hyperlipidaemia, another manifestation of the metabolic syndrome, can be associated with gout. A RCT has shown that fenofibrate, a hypolipidaemic agent, manifests uricosuric and urate lowering effects: its administration was associated with a 20% (14%, 26%) serum uric acid levels reduction with an ES of 1.13 (0.18, 2.07) and a 30% increase in serum uric acid clearance (47). Despite these results, there is no direct RCT evidence on the urate lowering properties of losartan and fenofibrates in gout, and therefore, their efficacy is yet to be demonstrated.

Conclusions. If possible, diuretic therapy is to be stopped in patients with gout and alternative antihypertensives are to be considered (*level IV*). Uricosuric and urate lowering effects has been shown with the use of both the antihypertensive losartan and the hypolipidaemic fenofibrate (levels IIb). However desirable their administration is in gout concomitant to hypertension or hyperlipidaemia, their clinical role and cost effectiveness in the treatment of gout is still under investigation.

■ DISCUSSION

This document presents the recommendations of the Italian Society of Rheumatology (SIR) for the management of patients with gout based on the 2006 EULAR recommendations (Tab. IV). Other recommendations have been recently published (60, 83, 84). The Italian recommendations however mainly addresses the need of adapting evidence to the current therapeu-

tic options available in Italy. The methodology of Italian recommendations mirrors the one assumed by the EULAR task force and has conserved its strengths.

The expert panel was appointed from the whole spectrum of healthcare professionals who could be involved in the management of patients with gout. The outcome of this selection can lead to compliance to these recommendations from clinicians of a different and complimentary background and therefore lead to improved management of gout and comorbidities in a more holistic manner.

The undertaken methodology presents various characteristics of strength which translated into the reliability of results. The review items on which to search for evidence were identified by the experts through a process of consensus with the aim of answering questions deemed relevant from a clinical perspective in the management of the patient with gout. New evidence on the pre-established items has been systematically collected via the Cochrane methodology utilising the same bibliographic research strategy of the EULAR recommendations, and integrating them with other strategies

Table IV - Propositions and relative strength of recommendation.

Recommendations	VAS (95% CI)	A-B%
Optimal treatment of gout requires both non-pharmacological and pharmacological modalities and should be tailored according to: 1. specific risk factors (levels of serum urate, previous attacks, changes in imaging); 2. clinical phase (acute/recurrent gout, intercritical gout, and chronic tophaceous gout); 3. general risk factors (age, sex, obesity, alcohol consumption, urate elevating drugs, drug interactions and comorbidity)	86 (79–93)	100
Patient education and appropriate lifestyle advice (healthy diet and reduced consumption of beverages containing fructose and alcohol, beer especially) are core aspects of management	83 (75–91)	86
Associated comorbidity and risk factors such as hyperlipidaemia, hypertension, hyperglycaemia, obesity and smoking should be addressed as an important part of the management of gout	85 (78–93)	93
Oral colchicine and/or NSAIDs, including COX-2 inhibitors, are first line agents for systemic treatment of acute gout. Corticosteroids are a convenient and well accepted option. However, comorbidities and contraindications are to be taken into account in the choice of treatment	93 (90–97)	100
Low-dose colchicine (up to 2 mg daily) is effective and safe for some patients with acute gout	86 (81–91)	93
Intra-articular aspiration and injection of a long acting steroid is an effective and safe treatment for an acute attack	86 (78–94)	93
Urate lowering therapy is indicated in patients with recurrent acute attacks, chronic arthropathy, tophi, or changes in imaging typical of gout	91 (87–95)	100
The therapeutic goal of urate lowering therapy is to promote crystal dissolution and prevent monosodium urate crystal formation. This is achieved by maintaining the serum uric acid below the saturation point for monosodium urate ($\leq 360 \mu\text{mol/L}$ or $\leq 6 \text{ mg/dL}$).	91 (87–95)	100
9. Allopurinol is an appropriate long-term urate lowering therapy. It should be started at a low dose (100 mg daily) and increased by 100 mg every two to four weeks if required. The dose must be adjusted in patients with renal impairment. If allopurinol toxicity occurs, options include uricosuric agents (when available) or other xanthine oxidase inhibitors	88 (82–94)	93
Febuxostat is an effective alternative to allopurinol which shows greater efficacy and minor adverse effects as urate lowering agent. Starting doses are to be low and increased if necessary	82 (76–89)	87
Prophylaxis against acute attack during the first months of urate lowering therapy can be achieved with colchicine (0.5 mg to 1mg daily) and/or NSAIDs. If not contraindicated, low-dose corticosteroids are a feasible alternative in refractory cases or cases of drug intolerance	87 (81–93)	93
When gout associates with diuretic therapy, stop the diuretic if possible. For hypertension and hyperlipidaemia consider the use of losartan and fenofibrate, respectively (both have modest uricosuric effects)	87 (82–92)	100

VAS, visual analogue scale; CI, confidence interval.

from Cochrane systematic reviews (85, 86). Such approach guarantees both consistency with the previously collected data and the required systematic methodology for the update with new evidence.

The strength of recommendation has been evaluated through the methodology recommended by the EULAR which assigns a level of evidence on the basis of a visual analogue scale and an ordinal scale. Such approach creates a summary of data on efficacy and safety which is combined with the clinical experience and therefore merges evidence and feasibility instead of merely providing grades of recommendations solely based on the design of the available studies.

The Italian recommendations include a number of limitations. Firstly, the review update has been only undertaken for a number of questions identified from the expert panel and therefore other questions assigned a level of priority inferior to the preestablished threshold were not considered. Among these, for example, were the queries on the efficacy and safety of antiplatelets other than aspirin, efficacy and safety of prophylactic low-dose corticosteroids during urate lowering treatment, the use of imaging technology in prognostic stratification and disease monitoring, the

effect of stopping urate lowering treatment in patients with optimal long-term control of gout and the establishment of target serum uric acid levels in urate lowering treatment.

A further limitation is the compilation of the literature review by a single reviewer. Additionally, the employment of validated scales for quality assurance was not ultimately utilised for a formal selection based on the level of quality acquired from this evaluation.

The Italian recommendations literature review has also identified sufficient lack of high level evidence in support of various treatment options which consequently leads to the adoption of different clinical approaches. Such variability translated in low strength of recommendation confidence interval precision for each proposition.

The experts believe that the future research agenda is to include a number of aspects which have not been yet enough investigated (Tab. V).

■ CONCLUSIONS

The Italian Society of Rheumatology (SIR) has developed an updated version of the

Table V - Future research agenda.

1	The best drug (colchicine, NSAID or corticosteroid), dose, and duration for prophylaxis of acute attacks when starting urate lowering treatment, and whether this should vary in different clinical settings (for example, in the presence of tophi) should be established
2	Further studies are necessary to determine treatment targets of serum uric acid levels in the different clinical circumstances: induction and short-term and long-term maintenance
3	Further studies are necessary to compare the efficacy, safety and cost effectiveness of allopurinol and newer xanthine oxidase inhibitors
4	Efficacy of educational programmes on lifestyle modifications (weight loss, reduced alcohol consumption, dietary purine restriction) in patients with gout is to be evaluated
5	Data on the possible benefits of urate lowering treatment in comorbid cardiovascular disease are to be further developed and supported with experimental evidence
6	The efficacy and safety profiles of various antiplatelet agents in hyperuricaemic patients are to be evaluated
7	The clinical significance of imaging of tissue uric acid depositions via various radiological modalities is yet to be formally evaluated
8	The efficacy and safety of long-term treatment with xanthine oxidase inhibitors is to be studied

EULAR recommendations for the management of patients with gout, adapted to the Italian healthcare system. Finally, 12 propositions were formulated to target the different levels of patient management: comorbidity and lifestyle, management of acute attacks and long-term management of gout. Propositions on long-term management based on the original EULAR recommendations were reformulated by considering the availability of new evidence and the Italian pharmaceutical formulary. The fact that the recommendations were formulated by a multidisciplinary team aids in ensuring good dissemination and their implementation will certainly improve the management of patients with a potentially curable disease such as gout.

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