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Recommendations and metaanalyses

2020 Recommendations from the French Society of Rheumatology for the management of gout: Management of acute flares

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ABSTRACT

Objective: To develop French Society of Rheumatology-endorsed recommendations for the management of gout flares.
Methods: These evidence-based recommendations were developed by 9 rheumatologists (academic or community-based), 3 general practitioners, 1 cardiologist, 1 nephrologist and 1 patient, using a systematic literature search, one physical meeting to draft recommendations and 2 Delphi rounds to finalize them.
Results: A set of 4 overarching principles and 4 recommendations was elaborated. The overarching principles emphasize the importance of patient education, including the need to auto-medicate for gout flares as early as possible, if possible within the first 12 h after the onset, according to a pre-defined treatment. Patients must know that gout is a chronic disease, often requiring urate-lowering therapy in addition to flare treatment. Comorbidities and the risk of drug interaction should be screened carefully in every patient as they may contraindicate some anti-inflammatory treatments. Colchicine must be early prescribed at the following dosage: 1 mg then 0.5 mg one hour later, followed by 0.5 mg, 2 to 3 times/day over the next days. In case of diarrhea, which is the first symptom of colchicine poisoning, dosage must be reduced. Colchicine dosage must also be reduced in patients with chronic kidney disease or taking drugs, which interfere with its metabolism. Other first-line treatment options are systemic/intra-articular corticosteroids, or non-steroidal anti-inflammatory agents (NSAIDs). IL-1 inhibitors can be considered as a second-line option in case of failure, intolerance or contraindication to colchicine, corticosteroids and NSAIDs. They are contraindicated in cases of infection and neutrophil blood count should be monitored.
Conclusion: These recommendations aim to provide strategies for the safe use of anti-inflammatory agents, in order to improve the management of gout flares.

1. Introduction

Gout is the most common type of inflammatory arthritis in Europe and worldwide, especially in men. In France, its prevalence has been estimated to 0.9% [1]. Epidemiological studies

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indicate that incidence and prevalence of gout are steadily increasing, especially in Western countries [2]. Gout results from chronic hyperuricemia and subsequent monosodium urate (MSU) crystals deposition within the joints, which are the cause of acute, recurrent and self-limiting attacks of arthritis [3]. Despite recent advances in the understanding of gout pathogenesis and therapeutic developments in recent years [4], gout remains largely under-diagnosed and poorly managed [5,6], including in France [7].

Acute gout flares are usually the first manifestation of the disease, and the first patient's reason for seeking care. Recent studies provided important insights into the management of these flares, and emphasized the critical need for a careful screening of comorbidities, which are common in gouty patients and may hold contraindications for several anti-inflammatory therapies [8]. Yet, studies consistently suggest that inadequate training of health professionals is a major barrier to care in gout [9,10]. In this context, evidence-based guidelines, like the 2016 European League Against Rheumatism (EULAR) recommendations [11], are needed to provide guidance to physicians in charge of gout care.

This first set of recommendations, promoted by the French Society of Rheumatology (Société française de rhumatologie, SFR), aimed at improving management of acute flares, by producing simple, easy to understand and memorize, up to date, evidence-based guidelines. They did not aim at an exhaustive coverage of flare management but focused on the most important part of management, taking into account French specificities and recent evidence. They are intended to all physicians involved in gout management, but primarily to general practitioners (GPs) and rheumatologists. A second part focuses on chronic management of gout and urate-lowering treatment.

2. Methods

The French Society of Rheumatology asked the convener (TB) to set up an ad hoc committee to design recommendations on gout management. The formed task force included 9 rheumatologists, 3 GPs, 1 nephrologist, 1 cardiologist and 1 patient from various parts of France and various practices (academic or private practice). The method we used followed the EULAR guidelines [12].

For the management of gout flares, an update of the systematic review of the literature (SLR) was performed by one of the committee member (AL) on all articles published from June 2013 (date of the SLR informing the last EULAR guidelines on gout) [11] to March 2019 in MedLine (via PubMed), covering all aspects of the management of gout flares and general safety data on available anti-inflammatory drugs, focusing on randomized controlled trials, large observational studies or meta-analysis. The quality of evidence was assessed by the GRADE method. The task force members then attended a 1-day meeting during which the results of the SLR were presented in an aggregated form and discussed, leading to draft a preliminary set of overarching principles and specific recommendations. After this meeting, the Delphi sequential voting technique was used to finalize the draft and reach consensus. Each participant rated his level of agreement for each recommendation by using an 11-point numerical rating scale (0, totally disagree; 10, fully agree) and could propose a reformulation of the recommendation. Each recommendation was accepted if all scores were ≥ 5 with a median ≥ 7. If not, or if a significant change in the formulation was made, new Delphi vote took place until acceptance of all recommendations.

The categories of evidence and strength of recommendations were determined according to the standards of the Oxford Centre for Evidence-Based Medicine [12].

Finally, the recommendations were presented and discussed at the 2019 SFR meeting and sent to a group of physicians composed of rheumatologists and GPs external to the task force who were asked to check their pertinence and clarity.

3. Results

The literature search yielded 2076 records (including duplicates), of which 232 abstracts were examined. Thirteen full-texts, including 3 RCTs, were reviewed and presented to the task force in addition to the SLR informing the 2016 EULAR guidelines. Two Delphi-rounds allowed reaching a consensus on the final set of 4 overarching principles and 4 recommendations (Table 1).

3.1. Overarching principles

3.1.1. Therapeutic education

A. The patient must know that it is essential to treat acute gout flare at the earliest symptom; he must be able to self-medicate according to a pre-established prescription previously fully explained by his physician.

Gout is characterized by recurrent acute inflammatory flares, with a brutal onset, extremely painful but transient, which typically involve the first metatarsophalangeal (MTP1) joint or the foot/ankle, leading to inability to walk [13]. Patients usually seek emergency care, yet they cannot always see a physician rapidly. Delay in appropriate drug initiation must be avoided by teaching patients self-management of their flares. Indeed, colchicine has been shown to be most effective when administered within the first 12 h of the flare [14], and there was expert agreement among the committee that all treatments of gout flares were more effective when applied early after the onset of flare. This implies that the treatment had been previously prescribed and fully explained to the patient by a physician. The "pill in the pocket" strategy to treat gout flares is recommended for all patients with gout.

B. The patient must know that gout management is not limited to the treatment of acute flares, and needs to know the importance of urate-lowering therapy (ULT), which is the only treatment able to relieve gout symptoms on the long term.

Gout is commonly perceived as an acute disease because flare resolution leads to return of the involved joints to normal, so that gout management is often focused on the sole flares [5]. However, flares result from chronic MSU crystals deposition, and bear a high risk of recurrence over time if crystalline deposits persist. A long-term treatment by urate-lowering drugs (ULDs) is required to obtain MSU crystal dissolution, which allows to prevent recurrent gout flares and other disease features, like tophi and urate arthropathy [3]. Patients must be informed that silent MSU crystal deposition persists after gout flare resolution, and that deposits require a long-term treatment to get dissolved. They should know that treating flares only will not cure gout.

3.1.2. Prerequisite for the therapeutic decision

C. Comorbidities (cardiovascular diseases, chronic kidney disease [CKD], diabetes mellitus, peptic ulcer, infections), history of drug-related adverse events and potential drug interaction, number and the type of joints involved, drive the choice of therapeutic options in the management of acute gout flare.

This principle recalls that the appropriate management of gout flare requires a holistic approach. Many comorbidities have been consistently associated with gout, including obesity, CKD, hypertension, type 2 diabetes, dyslipidemia, cardiovascular disease and stroke [15,16]; other comorbidities such as peptic ulcer and infections, are common in the general population, even if not associated with gout. Comorbidities and a number of co-prescribed drugs may contraindicate specific anti-inflammatory therapies and should be carefully screened before treating acute gout flares. A study

Table 1
Overarching principles and specific recommendations for the management of gout flares.

		Category of evidence	Strength of recommendation	Level of agreement (mean ± SD)
Overarching principles				
A	The patient must know that it is essential to treat acute gout flare at the earliest symptom; he must be able to self-medicate according to a pre-established prescription previously fully explained by his physician	4	C	9.79 ± 0.58
B	The patient must know that gout management is not limited to the treatment of acute flares, and needs to know the importance of urate-lowering therapy (ULT), which is the only treatment able to relieve gout symptoms on the long term	3	C	9.21 ± 0.97
C	Comorbidities (cardiovascular diseases, chronic kidney disease [CKD], diabetes mellitus, peptic ulcer, infections), history of drug-related adverse events and potential drug interaction, number and the type of joints involved, drive the choice of therapeutic options in the management of acute gout flare	3	C	9.71 ± 0.73
D	Colchicine, non-steroidal anti-inflammatory drugs (NSAIDs), oral or intra-articular corticosteroids, IL-1 inhibitors are the drugs that can be used for the management of acute gout flare. Other means may be associated: joint rest and cooling, analgesics	1B	A	9.50 ± 0.85
Specific recommendations				
1	Colchicine should be initiated as early as possible, ideally within the first 12 h, at the following dosage: 1 mg at the onset of the flare, followed by 0.5 mg one hour later, and continued on the following days at 0.5 mg × 2–3 per day depending on the course of the flare. In case of diarrhea, which is the first sign of toxicity, treatment should be decreased or stopped. The dosage of colchicine should be reduced in patients with impaired renal function and in the case of co-prescription of drugs that interfere with the metabolism of colchicine (https://www.drugbank.ca/drugs/DB01394)	1B	A	9.36 ± 0.84
2	Corticosteroids should be prescribed at the dose of 30 to 35 mg/d (prednisone equivalent) for 3–5 days. It is not recommended in patients with uncontrolled type 2 diabetes or high blood pressure. Intra-articular corticosteroids injections should be preferred for the treatment of mono-arthritis if the affected joint is easily accessible for a local procedure	1B	A	9.43 ± 0.76
3	NSAIDs should be prescribed orally and for a short period of time, the time of the flare only. They should be avoided in cases of stage 3–5 chronic kidney disease or severe cardiovascular disease	1A	A	9.00 ± 1.47
4	IL-1 inhibitors should be initiated in the hospital and prescribed only in cases of failure, intolerance or contraindication to NSAIDs, corticosteroids and colchicine. They are contraindicated in cases of infection and neutrophils blood count should be monitored	1A	A	9.36 ± 0.74

reported that almost 90% of patients with gout had at least one contraindication to non-steroidal anti-inflammatory drugs (NSAIDs), and one third of patients who received colchicine had at least one strong contraindication to the drug [8]. Flare characteristics may also drive treatment strategy. Local treatments (e.g., intra-articular injections) should be favored in cases of mono-articular involvement of a large joint (e.g., the knee) whereas systemic treatments appear as more relevant in flares involving difficult to access or multiple joints.

3.1.3. Available therapies

D. Colchicine, non-steroidal anti-inflammatory drugs (NSAIDs), oral or intra-articular corticosteroids, IL-1 inhibitors are the drugs that can be used for the management of acute gout flare. Other means may be associated: joint rest and cooling, analgesics.

This principle covers the scope of anti-inflammatory therapies available for the treatment of gout flares [17]. First-line options are colchicine, NSAIDs and corticosteroids that may be used alone or in combination; as there is no current efficacy data supporting the preferential use of one option over others, their choice is mostly driven by drug tolerance and/or contra-indications. IL-1 inhibitors are a second-line option [18]. Analgesics are often used as an adjuvant therapy in gout flares. One small open-label study reported that patients treated with topical ice therapy in combination with anti-inflammatory therapy (prednisone and colchicine, $n = 10$) experienced greater reduction in pain compared with patients not treated with ice ($n = 9$) over 1 week [19]. Local ice therapy has been shown to decrease the synovial levels of several pro-inflammatory cytokines (including IL-1ß and IL-6) in crystal-induced arthritis [20].

3.2. Recommendations

1. Colchicine should be initiated as early as possible, ideally within the first 12 h, at the following dosage: 1 mg at the onset of the flare, followed by 0.5 mg one hour later, and continued on the following days at 0.5 mg × 2–3 per day depending on the course of the flare. In case of diarrhea, which is the first sign of toxicity, treatment should be decreased or stopped. The dosage of colchicine should be reduced in patients with impaired renal function and in the case of co-prescription of drugs that interfere with the metabolism of colchicine (https://www.drugbank.ca/drugs/DB01394).

The efficacy of colchicine in gout flares has been demonstrated by two randomized placebo-controlled trials (RCTs) [21,22].

Importantly, the AGREE trial compared high doses (4.8 mg) to low doses (1.8 mg) of colchicine, started within the first 12 h of flare; the primary endpoint was a reduction ≥ 50% in pain scores within 24 h. In this trial, the low-dose regimen was as effective as the high-dose colchicine one (37.8% and 32.7% met the primary endpoint, respectively, vs. 15.5% in the placebo arm), but the safety of low-dose colchicine was markedly better, similar to that of placebo [22]. In France, colchicine is widely used [23] and available as 1 mg tablets, so the task force adapted the dosage of colchicine and recommended that 1 mg be given early after the flare, followed by 0.5 mg one hour later. The AGREE trial did not provide guidance for the following days. The committee recommended colchicine to be continued at a dosage of 0.5 mg 2 to 3 times a day according to tolerance, as long as flare symptoms persisted, usually for 3 to 5 days (expert consensus). Recently, the CONTACT trial compared colchicine 0.5 mg × 3 per day for 4 days to naproxen 750 mg/day for 7 days in patients with gout flares; the primary outcome was the change in pain intensity over the first 7 days. There was no difference between the two treatments in terms of efficacy, especially regarding the rapidity of action [24].

The most frequent adverse event reported in the AGREE trial was diarrhea, occurring in 76.9%, 23.0% and 13.6% of patients in the high-dose colchicine, low-dose colchicine and placebo groups, respectively [22]. In the CONTACT trial, diarrhea was reported in 45.9% of patients treated with colchicine 0.5 mg × 3/day vs. 20.0% in the naproxen group ($P < 0.001$) [24]. Digestive symptoms mimicking gastroenteritis (diarrhea, nausea, vomiting) are the first signs of colchicine poisoning, and dosage of colchicine must be reduced or colchicine should be stopped if they occur [25]. Indeed, colchicine poisoning may lead to fatal events such as severe pancytopenia, encephalopathy, myopathy, and renal, liver or cardiac failure [25]. Colchicine pharmacokinetics involves two major enzymes: P-Glycoprotein, responsible for its digestive and renal clearance; and CYP3A4, responsible for the metabolism of colchicine in hepatocytes [26]. Several commonly prescribed P-Glycoprotein/CYP3A4 inhibitors, such as cyclosporine, clarithromycin, verapamil or ketoconazole, increase colchicine plasma levels and expose patients to a higher risk of severe side effects [27]. The complete list of drugs interfering with colchicine metabolism can be found online: https://www.drugbank.ca/drugs/DB01394. The plasma levels of colchicine is also markedly increased by renal impairment, even more in severe cases (eGFR < 30 ml/min) [28]. In patients with renal failure, colchicine dosage must be reduced to levels insufficient to cure acute flares and alternative treatments must be considered.

As colchicine is known to be metabolized by the liver [26], dose reduction or avoidance is recommended in patients with hepatocellular insufficiency, although no study has specifically examined the pharmacokinetics of colchicine in this context.

2. Corticosteroids should be prescribed at the dose of 30 to 35 mg/d (prednisone equivalent) for 3–5 days. It is not recommended in patients with uncontrolled type 2 diabetes or high blood pressure. Intra-articular corticosteroids injections should be preferred for the treatment of mono-arthritis if the affected joint is easily accessible for a local procedure.

Two RCTs conducted in primary care settings compared prednisolone (30 mg/day for 5 days) to indomethacin (50 mg × 3/day for 2–3 days) and demonstrated that the two treatments were equivalent to relieve flare symptoms during the first 2 h after drug intake, and over 2 weeks [29,30]. However, in those studies, significantly more patients from the indomethacin groups experienced gastrointestinal adverse events as compared to the prednisolone groups. Another RCT, which compared prednisolone (35 mg/day for 5 days) to naproxen (500 mg × 2/day for 5 days), also showed similar efficacy over 90 h, and the safety profile was comparable across the two treatment arms [31]. It should be noted that no RCT compared the efficacy of systemic corticosteroids to placebo in the context of gout flare. However, on the basis of the results from those 3 RCTs, the task force recommended the use of oral corticosteroids (30–35 mg/day equivalent prednisolone for 3 to 5 days), which has been proved to be effective in the management of gout flares, but may worsen blood pressure or glycemic controls in hypertensive and diabetic patients respectively [32].

In addition, based on data from an open trial [33] and expert opinion, the use of intra-articular injection of corticosteroids is recommended over systemic corticosteroids in patients with mono-articular involvement of an easily accessible joint.

3. NSAIDs should be prescribed orally and for a short period of time, the time of the flare only. They should be avoided in cases of stage 3–5 chronic kidney disease or severe cardiovascular disease.

The use of NSAIDs in the management of gout flares has been extensively investigated and is supported by a recent meta-analysis [30,34], despite the fact that placebo-controlled trials have been scarce. The prescription of NSAIDs must be preceded by meticulous screening for cardiovascular risk factors or renal impairment. Indeed, in RCTs, the use of NSAIDs has been consistently associated with adverse events including upper gastrointestinal bleeding, cardiovascular events or renal impairment [35–37]. The increased cardiovascular risk associated with NSAIDs, including COX-2 selective inhibitors, has been confirmed by cohort studies and data from Canadian and European healthcare databases [38,39]. The risk of major cardiovascular events (including stroke) is increased within the first week of treatment, is the highest with diclofenac and during the first 30 days after NSAIDs initiation, and appears to be dose-dependent [38,39]. These data led the group to recommend strongly against the use of NSAIDs for the management of gout flares in cases of severe cardiovascular disease or stage 3-5 chronic kidney disease (eGFR < 60 ml/min). If NSAIDs are used, they should be for the shortest duration possible (i.e., the time of the flare only).

4. IL-1 inhibitors should be initiated in the hospital and prescribed only in cases of failure, intolerance or contraindication to NSAIDs, corticosteroids and colchicine. They are contraindicated in cases of infection and neutrophils blood count should be monitored.

Interleukin-1ß (IL-1ß) plays a pivotal role in the MSU crystal-induced inflammation [40]. One 150 mg subcutaneous injection of canakinumab, an anti-IL-1ß monoclonal antibody, has been found to be superior to triamcinolone acetonide (40 mg, one subcutaneous dose) to treat acute gout flares in patients with limited therapeutic options (i.e., contra-indication to NSAIDs and/or colchicine) [41]. The use of canakinumab was associated with an increased risk of severe adverse events compared to triamcinolone acetonide over 24 weeks, including infections (1.8% vs. 0%). These data led to the approval of canakinumab as a second-line option for the treatment of gout flares in Europe, only in patients with no infection and with severe gout, resistant or contraindicated to colchicine and NSAIDs, and in whom repeated corticosteroids treatments are not appropriate [18].

One recent RCT compared another IL-1 inhibitor, anakinra (100 mg daily in subcutaneous injections), to usual care (colchicine 0.5 mg up to three times daily, prednisone 35 mg/day or naproxen 500 mg up to twice daily) for the treatment of acute gout flares [42]. In this study, anakinra was non-inferior to usual treatments after 2 to 4 days, with a similar safety profile. This study adds to multiple case series supporting that this IL-1 receptor antagonist may be effective in the treatment of gout flares [43–46]. Importantly, a retrospective study in patients with stage 4–5 chronic kidney disease or kidney transplantation reported safe outcomes in this particular setting [47]. It should be noted that anakinra is not approved by European Medicines Agency for the treatment of gout flares.

Given that the cost of IL-1 inhibitors is much higher than colchicine, NSAIDs or corticosteroids, and that their use is associated with an increased risk of adverse events including infections, the task force considered IL-1 inhibitors as second-line agents in

the management of gout flares. There are currently no data on the cost-effectiveness of IL-1 blockers in the management of gout flares. Ongoing infection is an absolute contraindication to IL-1 inhibitors, and occult infections should be screened prior to initiation of these drugs, especially if they are long acting or to be used on the long term. In patients with severe renal impairment (eGFR < 30 ml/min) or on dialysis, lower doses of anakinra should be used (e.g., every other day) [48]. For these reasons, IL-1 blockers should be initiated at the hospital. The risk of neutropenia should also be monitored closely with long-term IL-1 inhibition.

4. Discussion

These recommendations, promoted by the SFR, are the first French guidelines for the management of gout. The treatment of hyperuricemia and the prophylaxis of flares are addressed in the second part of these guidelines. Overall, there was a good level of agreement on the present recommendations (Table 1), and only two Delphi rounds were necessary to reach consensus. With 4 overarching principles and 4 specific recommendations, these guidelines are voluntarily concise to facilitate their dissemination and implementation into daily practice among French physicians, and especially GPs and rheumatologists.

Gout often requires a multidisciplinary management. GPs and emergency physicians are first-line care providers for patients experiencing gout flares, and play as such a prominent role. Besides rheumatologists, other specialists like cardiologists and nephrologists are frequently confronted to the management of gout and its associated comorbidities. The involvement of patients in management is also crucial. The task force that made these recommendations thus included 3 GPs, 1 cardiologist, 1 nephrologist and 1 patient. Despite the central role of GPs in the management of gout flares, RCTs conducted in primary care are scarce and should be encouraged.

Management of gout has been worldwide estimated as suboptimal [6]. Studies have pointed out common mistakes, including prescription of inefficient drugs in the management of gout flares [49,50], stressing the importance of careful patient information. As stressed in the first overarching principle, the best way to implement early treatment for gout flares is to teach the patient how to treat a gout flare by himself, thus avoiding delays in reaching a physician. Information should also deal with the nature and doses of the drug to use, together with a prescription making it available to the patient and avoiding intake of inappropriate drugs. ULTs, which are a most important part of gout management, appear to be too unfrequently prescribed [7,51,52]. The common misperception of gout as an archetype of acute disease [5] appears as detrimental and should be corrected. It is important, when facing a patient who asks advice about a gout flare, to inform him about the necessity of a long-term urate-lowering treatment, as stressed in the second overarching principle of this guideline. Several tools may help delivering a comprehensive education to patients with gout: brochures, online resources or apps; their use should be considered in order to improve patients' knowledge of the disease and adherence to treatment [53,54].

The need to screen each patient for comorbidities is emphasized in the third principle. Comorbidities are frequent in gout, and only a small proportion of patients have few comorbidities [55,56]. As highlighted in the present guidelines, these comorbidities directly impact the choice of the anti-inflammatory drug to treat gout flare (Fig. 1). This has been particularly detailed with regard to colchicine, a drug characterized by a narrow therapeutic range. Recent pharmacokinetics studies provided insights on its metabolism and drug interactions [27]. Even though there is still insufficient data to produce precise dose adjustment recommendations, it appears that dose reduction in renal or hepatic impairment makes colchicine inappropriate for the management of gout flares in patients with such comorbidities. The same recommendation can be made with co prescription of drugs with strong pharmacokinetic interaction. According to Terkeltaub et al., in cases of concomitant treatment with strong P-Glycoprotein (e.g., cyclosporine) or CYP3A4 inhibitors (e.g., clarithromycin, ketoconazole, ritonavir), colchicine should be given at 0.5 mg the first day, a dose that should not be repeated earlier than 3 days after. In cases of moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil), colchicine should be given at 1 mg, and this dose should not be repeated earlier than 3 days after. No dose adjustment is required in cases of concomitant treatment with weak CYP3A4 inhibitors (e.g., azithromycin) [27].

Colchicine is the most commonly prescribed drug in acute gout flares especially in France [7,23], but the dose regimen that is commonly used, starting with 3 mg the first day, then 2 mg/day for one or two days, then 1 mg/day, should be abandoned, at least when colchicine is given early, in view of the AGREE trial results, which suggest the efficacy and good tolerance of the low-dose regimen recommended here [22]. As did the 2016 EULAR recommendations, the task force also recommends considering the association of anti-inflammatory drugs (i.e., colchicine and corticosteroids) in the management of gout flares [11]. This is based on expert opinion, and this strategy should be appropriately evaluated by future RCTs.

A Cochrane review reported overall a moderate evidence quality supporting the use of NSAIDs in gout flares [34]. This was mostly due to potential selection or reporting bias, but the authors of this review did not recommend against NSAIDs use in acute gout. Indeed, the efficacy of NSAIDs in various causes of inflammatory arthritis, including crystal-induced arthritis, is widely accepted. It should be noted that most trials evaluating NSAIDs in the context of acute gout used another NSAID or glucocorticoids as a comparator. The CONTACT trial indicates similar efficacy of naproxen 750 mg/day and low-dose colchicine (0.5 mg × 3/day) in the management of gout flares, but diarrhea was a frequent side effect of colchicine [24]. The present guidelines list NSAIDs as an option for gout flares, but emphasize the safety issues of these drugs in patients with gout. Indeed, numerous comorbidities of gout are also contraindications of NSAIDs, which are thus very common in this population [8]. In this regard, it should be noted that RCT evaluating oral corticosteroids used NSAIDs as active comparator, and that prednisolone 30 to 35 mg daily had a slightly better safety profile than NSAIDs (naproxen or indomethacin) for a short duration of treatment (i.e., up to 5 days) [29–31]. In patients with renal failure, steroids, which are seldom used in France [23], are obviously a valid option.

These guidelines also highlight the pivotal role of IL-1ß in gout flare pathophysiology [40]. This has led to the development of IL-1 inhibitors for the management and prophylaxis of acute gout flares [57]. These agents are interesting alternatives to colchicine, NSAIDs, and corticosteroids, in case contraindication or intolerance to these drugs. Importantly, the long-term prescription of the anti-IL-1ß monoclonal antibody canakinumab has been associated with a lower risk of cardiovascular events in patients with atherosclerotic disease, suggesting that IL-1ß inhibition could also improve cardiovascular outcomes [58]. However, these agents increase the risk of severe infections, and their price is much higher than other treatments of gout flares, so that they should be used as second-line agents only.

In conclusion, these first French evidence-based guidelines propose 4 overarching principles and 4 specific recommendations for the management of acute gout flares. The management of hyperuricemia and the prophylaxis of flares in patients initiating urate-lowering therapy are addressed elsewhere. These simple

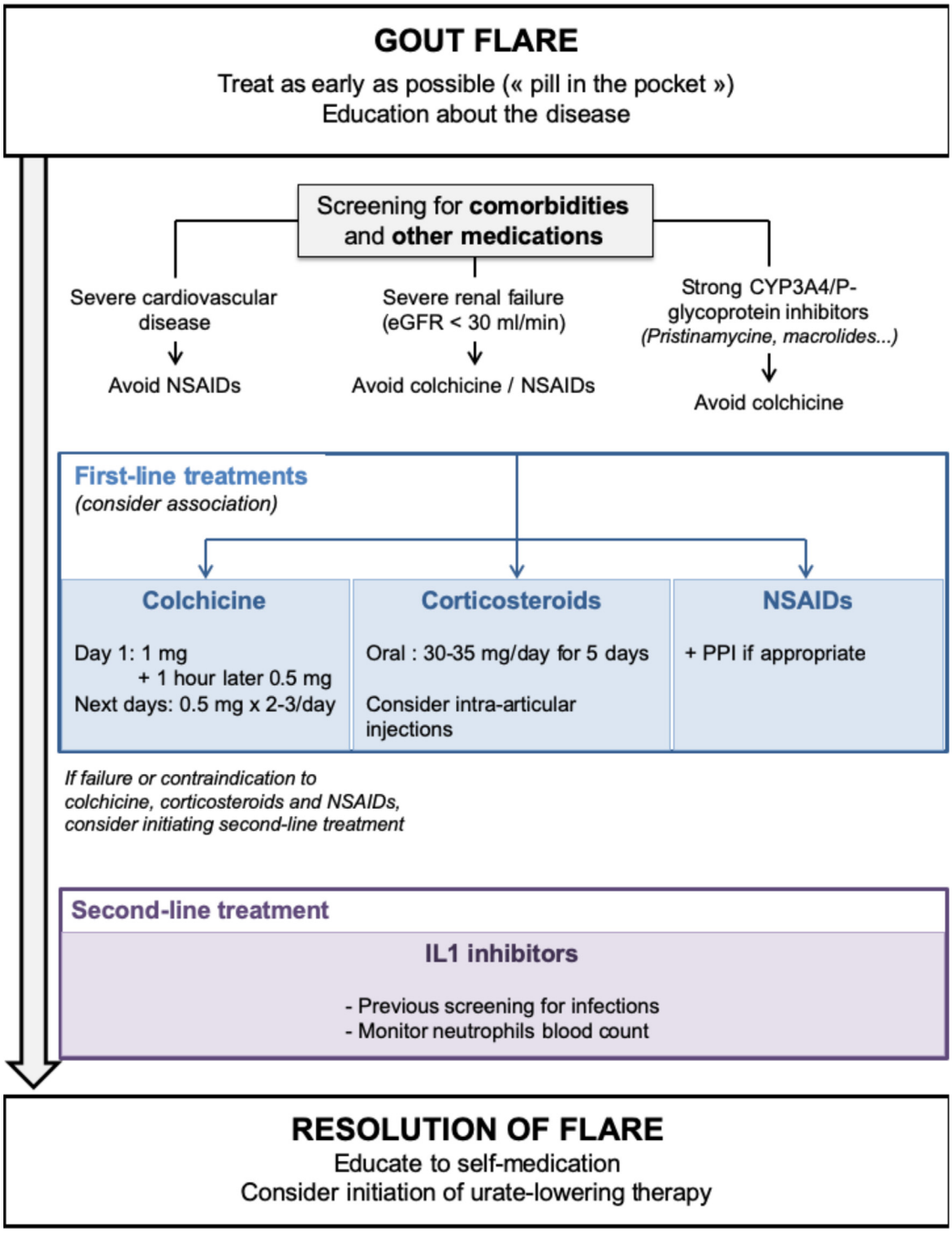

Fig. 1. Global strategy for the management of acute gout flares. eGFR, estimated glomerular filtration rate; IL1, interleukin 1; NSAIDs, non-steroidal anti-inflammatory drugs; PPI, proton pump inhibitor.

guidelines will need to be disseminated and their usefulness to be evaluated. They will also need to be updated over the next years according to advances on the topic, and the possible emergence of new drugs. The task force believes that the present recommendations and their dissemination and implementation should help physicians to improve the quality of gout care.

Disclosure of interest

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References

[1] Bardin T, Bouee S, Clerson P, et al. Prevalence of Gout in the Adult Population of France. Arthritis Care Res (Hoboken) 2016;68:261–6.
[2] Kuo CF, Grainge MJ, Zhang W, et al. Global epidemiology of gout: prevalence, incidence and risk factors. Nat Rev Rheumatol 2015;11:649–62.
[3] Dalbeth N, Merriman TR, Stamp LK. Gout. Lancet 2016;388:2039–52.
[4] Pascart T, Liote F. Gout: state of the art after a decade of developments. Rheumatology (Oxford) 2019;58:27–44.
[5] Doherty M, Jansen TL, Nuki G, et al. Gout: why is this curable disease so seldom cured? Ann Rheum Dis 2012;71:1765–70.
[6] Kuo CF, Grainge MJ, Mallen C, et al. Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study. Ann Rheum Dis 2015;74:661–7.
[7] Goossens J, Lancrenon S, Lanz S, et al. GOSPEL 3: Management of gout by primary-care physicians and office-based rheumatologists in France in the early 21st century - comparison with 2006 EULAR Recommendations. Joint Bone Spine 2017;84:447–53.
[8] Keenan RT, O'Brien WR, Lee KH, et al. Prevalence of contraindications and prescription of pharmacologic therapies for gout. Am J Med 2011;124:155–63.
[9] Spencer K, Carr A, Doherty M. Patient and provider barriers to effective management of gout in general practice: a qualitative study. Ann Rheum Dis 2012;71:1490–5.
[10] Vaccher S, Kannangara DR, Baysari MT, et al. Barriers to Care in Gout: From Prescriber to Patient. J Rheumatol 2016;43:144–9.
[11] Richette P, Doherty M, Pascual E, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. Ann Rheum Dis 2017;76:29–42.
[12] van der Heijde D, Aletaha D, Carmona L, et al. 2014 Update of the EULAR standardised operating procedures for EULAR-endorsed recommendations. Ann Rheum Dis 2015;74:8–13.
[13] Taylor WJ, Fransen J, Jansen TL, et al. Study for Updated Gout Classification Criteria: Identification of Features to Classify Gout. Arthritis Care Res (Hoboken) 2015;67:1304–15.
[14] Terkeltaub RA. Colchicine update: 2008. Semin Arthritis Rheum 2009;38:411–9.
[15] Bardin T, Richette P. Impact of comorbidities on gout and hyperuricaemia: an update on prevalence and treatment options. BMC Med 2017;15:123.
[16] Kuo CF, Grainge MJ, Mallen C, et al. Comorbidities in patients with gout prior to and following diagnosis: case-control study. Ann Rheum Dis 2016;75:210–7.
[17] Latourte A, Bardin T, Richette P. Prophylaxis for acute gout flares after initiation of urate-lowering therapy. Rheumatology (Oxford) 2014;53:1920–6.
[18] https://www.has-sante.fr/upload/docs/application/pdf/2014-05/ilaris_pic_ei_goutte_avis3_modifie_ct13361.pdf.
[19] Schlesinger N, Detry MA, Holland BK, et al. Local ice therapy during bouts of acute gouty arthritis. J Rheumatol 2002;29:331–4.
[20] Guillot X, Tordi N, Laheurte C, et al. Local ice cryotherapy decreases synovial interleukin 6, interleukin 1beta, vascular endothelial growth factor, prostaglandin-E2, and nuclear factor kappa B p65 in human knee arthritis: a controlled study. Arthritis Res Ther 2019;21:180.
[21] Ahern MJ, Reid C, Gordon TP, et al. Does colchicine work? The results of the first controlled study in acute gout. Aust N Z J Med 1987;17:301–4.
[22] Terkeltaub RA, Furst DE, Bennett K, et al. High versus low dosing of oral colchicine for early acute gout flare: Twenty-four-hour outcome of the first multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison colchicine study. Arthritis Rheum 2010;62:1060–8.
[23] Rozenberg S, Lang T, Laatar A, et al. Diversity of opinions on the management of gout in France. A survey of 750 rheumatologists. Rev Rhum Engl Ed 1996;63:255–61.
[24] Roddy E, Clarkson K, Blagojevic-Bucknall M, et al. Open-label randomised pragmatic trial (CONTACT) comparing naproxen and low-dose colchicine for the treatment of gout flares in primary care. Ann Rheum Dis 2020;79:276–84.
[25] Finkelstein Y, Aks SE, Hutson JR, et al. Colchicine poisoning: the dark side of an ancient drug. Clin Toxicol (Phila) 2010;48:407–14.
[26] Slobodnick A, Shah B, Krasnokutsky S, et al. Update on colchicine, 2017. Rheumatology (Oxford) 2018;57:i4–11.
[27] Terkeltaub RA, Furst DE, Digiacinto JL, et al. Novel evidence-based colchicine dose-reduction algorithm to predict and prevent colchicine toxicity in the presence of cytochrome P450 3A4/P-glycoprotein inhibitors. Arthritis Rheum 2011;63:2226–37.
[28] Wason S, Mount D, Faulkner R. Single-dose, open-label study of the differences in pharmacokinetics of colchicine in subjects with renal impairment, including end-stage renal disease. Clin Drug Investig 2014;34:845–55.
[29] Man CY, Cheung IT, Cameron PA, et al. Comparison of oral prednisolone/paracetamol and oral indomethacin/paracetamol combination therapy in the treatment of acute goutlike arthritis: a double-blind, randomized, controlled trial. Ann Emerg Med 2007;49:670–7.
[30] Rainer TH, Cheng CH, Janssens HJ, et al. Oral Prednisolone in the Treatment of Acute Gout: A Pragmatic, Multicenter, Double-Blind, Randomized Trial. Ann Intern Med 2016;164:464–71.
[31] Janssens HJ, Janssen M, van de Lisdonk EH, et al. Use of oral prednisolone or naproxen for the treatment of gout arthritis: a double-blind, randomised equivalence trial. Lancet 2008;371:1854–60.
[32] Richette P, Bardin T. Should prednisolone be first-line therapy for acute gout? Lancet 2008;372:1301 [author reply -2].
[33] Fernandez C, Noguera R, Gonzalez JA, et al. Treatment of acute attacks of gout with a small dose of intraarticular triamcinolone acetonide. J Rheumatol 1999;26:2285–6.
[34] van Durme CM, Wechalekar MD, Buchbinder R, et al. Non-steroidal anti-inflammatory drugs for acute gout. Cochrane Database Syst Rev 2014;16:CD010120.
[35] Coxib, traditional NTC, Bhala N, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet 2013;382:769–79.
[36] Nissen SE, Yeomans ND, Solomon DH, et al. Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis. N Engl J Med 2016;375:2519–29.
[37] Trelle S, Reichenbach S, Wandel S, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. BMJ 2011;342:c7086.
[38] Bally M, Dendukuri N, Rich B, et al. Risk of acute myocardial infarction with NSAIDs in real world use: bayesian meta-analysis of individual patient data. BMJ 2017;357:j1909.
[39] Schmidt M, Sorensen HT, Pedersen L. Diclofenac use and cardiovascular risks: series of nationwide cohort studies. BMJ 2018;362:k3426.
[40] Martinon F, Petrilli V, Mayor A, et al. Gout-associated uric acid crystals activate the NALP3 inflammasome. Nature 2006;440:237–41.
[41] Schlesinger N, Alten RE, Bardin T, et al. Canakinumab for acute gouty arthritis in patients with limited treatment options: results from two randomised, multicentre, active-controlled, double-blind trials and their initial extensions. Ann Rheum Dis 2012;71:1839–48.
[42] Janssen CA, Oude Voshaar MAH, Vonkeman HE, et al. Anakinra for the treatment of acute gout flares: a randomized, double-blind, placebo-controlled, active-comparator, non-inferiority trial. Rheumatology (Oxford) 2019;58:1344–52.
[43] Chen K, Fields T, Mancuso CA, et al. Anakinra's efficacy is variable in refractory gout: report of ten cases. Semin Arthritis Rheum 2010;40:210–4.
[44] Ghosh P, Cho M, Rawat G, et al. Treatment of acute gouty arthritis in complex hospitalized patients with anakinra. Arthritis Care Res (Hoboken) 2013;65:1381–4.
[45] Ottaviani S, Molto A, Ea HK, et al. Efficacy of anakinra in gouty arthritis: a retrospective study of 40 cases. Arthritis Res Ther 2013;15:R123.
[46] So A, De Smedt T, Revaz S, et al. A pilot study of IL-1 inhibition by anakinra in acute gout. Arthritis Res Ther 2007;9:R28.
[47] Loustau C, Rosine N, Forien M, et al. Effectiveness and safety of anakinra in gout patients with stage 4-5 chronic kidney disease or kidney transplantation: A multicentre, retrospective study. Joint Bone Spine 2018;85:755–60.
[48] https://www.has-sante.fr/upload/docs/evamed/CT-17195_KINERET_PIC_EIT_Avis2_CT17195.pdf.
[49] Neogi T, Hunter DJ, Chaisson CE, et al. Frequency and predictors of inappropriate management of recurrent gout attacks in a longitudinal study. J Rheumatol 2006;33:104–9.
[50] Pascart T, Lancrenon S, Lanz S, et al. GOSPEL 2 - Colchicine for the treatment of gout flares in France - a GOSPEL survey subgroup analysis. Doses used in common practices regardless of renal impairment and age. Joint Bone Spine 2016;83:687–93.
[51] Kuo CF, Grainge MJ, Mallen C, et al. Eligibility for and prescription of urate-lowering treatment in patients with incident gout in England. JAMA 2014;312:2684–6.
[52] Richette P, Flipo RN, Patrikos DK. Characteristics and management of gout patients in Europe: data from a large cohort of patients. Eur Rev Med Pharmacol Sci 2015;19:630–9.
[53] Gossec L, Molto A, Romand X, et al. Recommendations for the assessment and optimization of adherence to disease-modifying drugs in chronic inflammatory rheumatic diseases: a process based on literature reviews and expert consensus. Joint Bone Spine 2019;86:13–9.
[54] Zangi HA, Ndosi M, Adams J, et al. EULAR recommendations for patient education for people with inflammatory arthritis. Ann Rheum Dis 2015;74:954–62.
[55] Richette P, Clerson P, Perissin L, et al. Revisiting comorbidities in gout: a cluster analysis. Ann Rheum Dis 2015;74:142–7.
[56] Zhu Y, Pandya BJ, Choi HK. Comorbidities of gout and hyperuricemia in the US general population: NHANES 2007–2008. Am J Med 2012;125 [679-87 e1].
[57] So A. IL1 inhibition in gout-where are we a decade on? Arthritis Res Ther 2019;21:233.
[58] Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. N Engl J Med 2017;377:1119–31.