2020 recommendations from the French Society of Rheumatology for the management of gout: Urate-lowering therapy

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Tristan Pascart[a], Augustin Latourte[b], René-Marc Flipo[c], Gérard Chalès[d], Laurence Coblentz-Baumann[e], Alain Cohen-Solal[f], Hang-Korng Ea[b], Jacques Grichy[g], Emmanuel Letavernier[h], Frédéric Lioté[b], Sébastien Ottaviani[i], Pierre Sigwalt[b], Guy Vandecandelaere[j], Pascal Richette[b], Thomas Bardin[b]

(a) Service de Rhumatologie, GH de l'Institut Catholique de Lille, Université de Lille, Lille, France ; EA4490, Physiopathologie des maladies osseuses inflammatoires, Université de Lille, Lille, France

(b) Service de Rhumatologie, Hôpital Lariboisière, AP-HP, Paris, France ; Inserm U1132 BIOSCAR, Université de Paris, Paris, France

(c) Service de Rhumatologie, CHU de Lille, Université de Lille, Lille, France

(d) Faculté de Médecine de Rennes, Rennes, France

(e) Département de Médecine Générale, Université de Paris, Paris, France

(f) Service de Cardiologie, Hôpital Lariboisière, AP-HP, Paris, France ; Inserm U942 MASCOT, Université de Paris, Paris, France

(g) Exercice libéral, Montlignon, France

(h) Service de Physiologie, Hôpital Tenon, AP-HP, Paris, France ; Inserm U1155, UPMC Université Paris 6, Sorbonne Universités, Paris, France

(i) Service de Rhumatologie, Hôpital Bichat, AP-HP, Paris, France

(j) Exercice libéral, Saint-Omer, France

Corresponding author : Pr Thomas Bardin, Service de Rhumatologie, Hôpital Lariboisière, 2 rue Ambroise Paré, 75010 Paris, France. Tél : +33-1-49-95-62-90 ; Fax : +33-1-49-95-86-31 ; thomas.bardin@aphp.fr

Abstract

Objective. To develop French Society of Rheumatology-endorsed recommendations for the management of urate-lowering therapy (ULT).

Methods. 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 two Delphi rounds to finalize them.

Results. A set of 3 overarching principles and 5 recommendations was elaborated. The overarching principles emphasize the importance of patient education, especially the need for explaining the objective of lowering serum urate (SU) level to obtain crystal dissolution, clinical symptoms disappearance and avoidance of complications. ULT is indicated as soon as the diagnosis of gout is established. SU level must be decreased below 300 µmol/L (50mg/L) in all gout patients or at least below 360 µmol/L (60 ml/l) when the 300 µmol/L target cannot be reached, and must be maintained at these targets and monitored life-long. The choice of the ULT primarily relies on renal function: in patients whose estimated glomerular filtration rate (eGFR) is above 60ml/min/1.73m^2, first-line ULT is allopurinol; in those with eGFR is between 30 and 60ml/min/1.73m^2, allopurinol use must be cautious and febuxostat can be considered as an alternative; and in those whose eGFR is below 30ml/min/1.73m^2, allopurinol must be avoided and febuxostat should be preferred. Prophylaxis of ULT-induced gout flares involves progressive increase of ULT dosage and low-dose colchicine for at least 6 months. Cardiovascular risk factors and diseases, the metabolic syndrome and chronic kidney disease must be screened and managed.

Conclusion. These recommendations aim to provide simple and clear guidance for the management of ULT in France.

Keywords: Gout, urate lowering therapy, allopurinol, febuxostat, prophylaxis, education

Introduction

Gout is caused by the presence of monosodium urate (MSU) crystals formed during the course of prolonged hyperuricemia [1, 2]. It is the most common form of inflammatory arthritis with a prevalence of 0.9% of the adult population of France [3]. Gout causes recurrent highly painful bouts of arthritis (gout flares [2]) and can lead to the development of debilitating tophi and destructive arthropathy when left untreated. The disease is commonly associated with renal, metabolic and cardiovascular comorbidities which impair the prognosis of gout patients [4, 5]. The aim of the long-term treatment of gout is to prevent the occurrence of flares and complications of the disease, by dissolving the pathogenic crystals.

Several national and international rheumatology societies have produced guidelines for the management of gout over the recent years, among which the American College of Rheumatology (ACR), European League Against Rheumatisms (EULAR), and the British Society of Rheumatology (BSR) with some discrepancies between them due to different local habits and the general lack of firm scientific data [6-9]. The paucity of unquestionable evidence-based data also led to the production of controversial guidelines by the American College of Physicians which defended a very different strategy than Rheumatology societies, whereas primary care physicians (PCPs) are in first-line for the management of gout in a vast majority of patients [10, 11]. Alike in other countries, gout management in France is known to be highly suboptimal [12, 13], and gout patients are still seen with active diseases despite long-standing diagnoses [14]. French physicians had not been provided with a specific National guidance for the management of gout so far.

The aim of this work was to provide French physicians, with recommendations for the urate-lowering management of gout that would take into account updated evidence since the 2016 EULAR guidelines and French specificities. Recommendations on the management of gout flares have been produced in a first article [15].

Methods

The French Society of Rheumatology (Société Française de Rhumatologie, SFR), convened a task force of 9 rheumatologists (in academic or private practice), three GPs, one nephrologist, one cardiologist and one patient. The starting point of the work was the 2016 EULAR guidelines [8]. An update of the systematic literature review (SLR) covering the time-period between January 2016 and April 2019 was performed by a task-force member (TP). The SLR involved searches of MedLine (via PubMed) covering all aspects related to gout long-term management, with a particular focus on the tolerance, efficacy, renal and cardiovascular effects of available urate-lowering treatments (ULTs), relying preferentially on randomized control trials (RCTs) or large well conducted observational studies. The quality of evidence was assessed by the GRADE method. Next, the task force members attended a 1-day meeting during which results of the SLR were presented in an aggregated form. The task force debated and evaluated the presented evidence, then formulated a preliminary set of over-arching principles and recommendations, with the aim of retaining only the most important aspects of long-term gout management, to provide simple and easily understandable recommendations. Consensus for each over-arching principle and recommendation was then searched using the Delphi methods, undertaken by email after the face to face meeting. Each participant was asked to rate his level of agreement (LoA) with each final recommendation using a 11-point numerical rating scale (0, totally disagree; 10, fully agree) and could propose modifications of the sentencing 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(s) took place until acceptance of all recommendations.

The recommendations were finally 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.

Results

The literature search yielded 2143 records (including duplicates), of which 128 abstracts were examined. Ninety-one full-texts were reviewed and presented to the task force (Figure 1). Two Delphi rounds allowed reaching a consensus on the final set of 3 over-arching principles and 5 recommendations (Table 1).

Overarching principles

A. *Information and education of the patient are essential for success of long-term management of gout. (task force agreement 10.0 ± 0/10, level of evidence 1b, Grade of recommendation A)*

Recent evidence clearly showed that well informed and educated gout patients can be effectively treated [16]. Patients must be actors of the management of their disease and should be well educated in that prospect, particularly during the first visits [17].

B. *The gout patient needs to know that flares are related to chronic monosodium urate crystal deposits and that the goal of the treatment is the permanent decrease of the serum urate level to obtain complete dissolution of these deposits, for clinical symptoms to disappear and to prevent chronic complications of gout.*
(task force agreement 9.77 ± 0.62/10, level of evidence 2a, 4, Grade of recommendation B-D)

It is well known that MSU crystals are responsible for gout. Crystals trigger gout flares mainly through the activation of the inflammasome [18], accumulate in tophi and cause gouty bone erosions. Patients must understand that getting rid of these crystals will ultimately lead to the disappearance of gout flares, tophi, and to the avoidance or improvement of urate arthropathy. Patients should also be informed that dissolution of MSU crystals is made possible by the long term decrease of serum urate (SU)[19] concentration to levels well below the saturation point of monosodium urate [20].

C. The treating physician needs to take the time to inform the patient about:

1. The importance of reaching the serum urate level target to allow for the dissolution of MSU crystals

2. The importance of the long-term adherence of urate lowering therapy

3. The risk of gout flares during the introduction of urate-lowering therapy

4. The cardiovascular, metabolic and renal risks associated with gout

5. The necessary adaptations of daily habits (avoid alcohol and sugar-sweetened beverage consumption, encourage regular physical activity and weight loss)

(task force agreement 9.54 ± 0.90/10, level of evidence 2a,2c, Grade of recommendation B)

Taking time to inform the patients on the various aspects of the disease has a central role in the success of the long-term treatment of gout [16, 17, 21]. The task force did bear in mind that this time-consuming delivery of information was difficult in clinical practice especially for GPs and specialists in private practices, and could therefore be spread across the first initial visits. It is well recognized that MSU crystal dissolution is a slow process which starts once the SU target is reached [22, 23] and requires long-term adherence to the hypouricemic medications. With increasing data on the poor adherence of gout patients [24, 25] and the importance of information to improve this adherence on the long-term, the task force insisted that this effort should be made early in the course of the management [17, 21]. ULT initiation is known to increase the risk of gout flares. Patients‘ knowledge of this transient risk helps preventing self-interruption of their treatment when facing flares [26]. Patients must also understand that gout is a serious disease, with associated comorbidities that have an impact on their quality of life and mortality [5, 27-30]. Dietary efforts should be focused on avoiding alcohol, including beer with/without alcohol, and fructose-sweetened beverage consumption, weight reduction in over weighted patients, as these factors have the highest

impacts on SU, even though the improvement obtained by life style modification remains modest [31, 32].

Recommendations

1. *A permanent urate-lowering therapy is indicated as soon as the diagnosis of gout is established.*

   (task force agreement 9.75 ± 0.65/10, level of evidence 4, Grade of recommendation D)

Any drug prescription first requires a careful evaluation of its benefits/risks ratio to be made. Urate lowering drugs (ULDs) expose patients to side effects and do not escape to this general rule. Previous guidelines therefore requested sets of severity items to be identified before considering ULD introduction (number of flares, tophi, urolithiasis, chronic kidney diseases, young age, cardiovascular comorbidities…) and did not recommend the use of ULDs from the first flare [6, 8, 9]. However, our perception of gout has changed, in particular with the knowledge that gout might be an independent risk factor for premature death [33, 34] and that cardiovascular and renal diseases and risk factors accumulate with time [35], making the late management of gout difficult [27]. Furthermore, delaying ULD introduction allows crystal deposits to grow and makes their dissolution under ULDs slower. Keeping these data in mind, the task force unanimously felt that recommending a systematic introduction of ULT drugs once the diagnosis of gout has been made would prevent the chronic worsening of gout. In addition, gout flares generally induce excruciating pain and the patient who was part of this committee, as the ones involved in the EULAR recommendations [8], wished to get rid of the risk of recurrences as early as possible. Indicating ULDs as soon as the diagnosis of gout has been definitely obtained also simplifies the message, and avoids referring to a complicated list of items, which may lead to under-treatment. In contrast, there is no definite evidence that treating asymptomatic hyperuricemia provides clinical benefits, whereas the risk of side effects remains at

least the same, so that the task force required the diagnosis of gout to be certain to indicate ULDs, and did not recommend indication of ULDs in asymptomatic hyperuricemia.

2. *Serum urate level must be decreased below 360 µmol/L (60 mg/L) and if possible, below 300 µmol/L (50 mg/L) in all gout patients. Once the target is reached, treatment must be maintained, and serum urate levels must be monitored once or twice yearly.*
   (task force agreement 9.77 ± 0.45/10, level of evidence 2b, 3a, Grade of recommendation B-C)

MSU crystal dissolution is a slow process. Dual-energy computed tomography (DECT) follow-up studies showed that MSU crystal depletion was incomplete even after 2 years of treatment when the SU target had been set at below 360 µmol/L [22, 23]. Given the relationship between MSU crystal burden and the risk of gout flares [36, 37] and the fact that, in the only trial showing a clear relationship between SU level reduction and decrease of gout flares, patients had in a vast majority reached a SU level below 300 µmol/L [16], the task force recommended the objective of an SU level below 300 µmol/L for all gout patients. This target should not be limited to patients with clinical subcutaneous tophi, but should be generalized in order to reduce the time of persistence of MSU crystals in all gout patients. Even at fixed doses of ULT, SU levels may change, and monitoring of SU is warranted, although whether this monitoring should be done once or twice a year remains unclear [38].

3. *Choice of urate lowering drugs:*
   - *When the eGFR is above 60 ml/min/1.73m^2, first-line urate-lowering treatment is allopurinol. The starting dose of allopurinol is 50-100 mg per day, to be increased by steps of 50 to 100 mg every 2 to 4 weeks until the serum urate target is reached.*

- *When the eGFR is 30 to 60 ml/min/1.73m^2, allopurinol use must be cautious and febuxostat can be considered an alternative.*
- *When the eGFR is below 30 ml/min/1.73m^2, allopurinol must be avoided and febuxostat should be preferred.*
- *Febuxostat use must be cautious for patients with severe cardiovascular diseases.*

(task force agreement 9.08 ± 1.04/10, level of evidence 1b, 4, Grade of recommendation A-D)

Because of its long experience of use, proven efficacy and low price, allopurinol remains the first choice of ULDs in patients with normal renal function. Severe cutaneous adverse reactions (SCARs) are the most dreaded side effects of allopurinol; the rule of using a low starting dose progressively increased until the desirable target is obtained should be applied, as several studies have shown that this conduct reduced SCAR incidence [39]. Renal failure has been considered for long as a risk factor for SCARs leading to adjust the maximal dose of allopurinol to creatinine clearance [40]. Even if this historical rule has been recently contested [41], caution remains in order in prescribing allopurinol to chronic kidney disease (CKD) patients, and the drug should be avoided in patients with estimated glomerular filtration rate (eGFR) below 30ml/min/1.73m^2.

Febuxostat appears as a valid alternative to allopurinol in CKD patients, because the drug is only partially excreted by the kidney. In our opinion febuxostat can even be carefully used in patients with eGFR below 30ml/min/1.73m^2, in whom it appears to keep its efficacy and safety profiles according to several studies, although these studies were rather small and, for most of them, retrospective [42, 43]. The use of febuxostat in patients with a history of severe cardiovascular disease is discouraged by the recent results of the CARES trial, that highlighted an increased mortality rate in such patients treated by febuxostat versus those who received allopurinol [44] and by the risk of cardiovascular events when febuxostat is suddenly stopped in these patients [45]. Severe cardiovascular disease was defined as a history of myocardial infarction or unstable angina, transient ischemic attack,

cerebrovascular event, peripheral artery disease, coronary or carotid revascularization or complicated diabetes mellitus. The committee suggests that a complementary advice from a cardiologist should be gathered when treatment with febuxostat is however considered in situations of prior severe cardiovascular disease.

In patients whose eGFR is between 30 and 60 ml/min/1.73m^2, and particularly in those with a cardiovascular history, allopurinol can be chosen, but its use demands increased caution: the initial dose should be lower (50 mg/d), follow-up should be closer, and dose increase should be slower, especially if a dosage above the one authorized by creatinine clearance is needed to reach the uricemia target. Recent evidence indeed suggests that increasing allopurinol doses above renal limitations could be effective and well tolerated, even though, due to their small sampling size and the rarity of SCARs, the supporting studies could not bring complete reassurance on the safety of this conduct [46, 47].

4. *Prophylaxis of gout flares induced with the initiation of urate-lowering therapy:*
    - *Flares must be prevented as soon as urate-lowering therapy is started, with the association of a 0.5 to 1 mg daily dose of colchicine for at least 6 months in the absence of contraindications and by starting low and progressively increasing doses of the urate lowering drug.*

(task force agreement 9.62 ± 0.79, level of evidence 1c, Grade of recommendation A)

ULT initiation is commonly associated with increased risk of flares, as compared to placebo, which eventually improves 6 to 12 months after SU target is reached [16]. Recent evidence showed that low starting doses of ULT drugs and subsequent progressive increases of doses were efficient to lower the risk of gout flares for both allopurinol and febuxostat [16, 48]. Low dose colchicine has also been shown to decrease the number of ULD-induced flares [49]. The toxicity of colchicine is increased in patients with renal failure [50] or with drugs that interfere with colchicine metabolism, especially

cyclosporine, ketoconazole, macrolides, ritonavir and, to a lesser extent, verapamil [51, 52]. In these settings, close monitoring of side effects and reduction of colchicine dosage (i.e. 0.5 mg every other day in patients with moderate CKD) should be done. Avoidance of colchicine in those with terminal renal failure or with colchicine-induced side effects are supported by common sense but the committee was unable to provide more specific guidance due to the lack of precise data.

5. *Gout comorbidities:*

    - *Cardiovascular risk factors and diseases, metabolic syndrome and chronic kidney disease must be screened and managed*.

(task force agreement 9.85 ± 0.58/10, level of evidence 4, Grade of recommendation D)

Gout is a chronic metabolic condition frequently associated with comorbidities, including hypertension, type 2 diabetes, dyslipidemia, renal and cardiovascular diseases, which worsen the poorer prognosis of gout patients as compared to the general population [5]. Appropriate diagnosis and management of these life-threatening conditions is of obvious importance. Furthermore, some comorbidities are causal of hyperuricemia, particularly obesity and hypertriglyceridemia, and their management is also of importance for the decrease of SU levels [53, 54]. Management of comorbidities also provides the opportunity to replace, whenever possible, drugs that increase SU levels (thiazide and loop diuretics, beta-blockers, low dose aspirin, cyclosporine, tacrolimus, pyrazinamide, ethambutol) by drugs with SU lowering properties (losartan, fenofibrate, atorvastatin, amlodipine) [55-57]. Screening, managing and monitoring CKD is central in the management of gout, first because of the causal relationship between decreased renal function and increased SU levels, and second for the choice of treatments for flares, flare prophylaxis and ULDs which are guided by the level of CKD [58] (Figure 2).

Discussion

Gout is a frequent and serious disease. Mismanagement is common [12], and mismanaged or neglected gout increasingly becomes a very severe disease that strongly impairs quality of life [59, 60] and function [61], decreases life expectancy [34], and associates with comorbidities [30] which frequently makes its treatment challenging [27]. This situation is difficult to accept as gout is the best understood and most curable rheumatological condition, and targeted urate-lowering allows dissolution of MSU crystals and disappearance of gout features. In an attempt to improve gout management in France, the SFR decided to promote simple and easily readable recommendations aiming at rheumatologists, but also at GPs who take care of most gouty patients in our country. This set of SFR recommendations on the chronic management of gout was voluntarily limited to three overarching principles and 5 recommendations. It was not intended to be extensive but focused on the most important points the committee felt worth being highlighted to improve the management of gout.

Patient education appears as a key to success of long-term gout management and its outmost importance was highlighted in the overarching principles of the present recommendations. Gout is generally misbelieved to be an acute disease, mainly responsible for flares, which are very painful but transient, and followed by a full recovery of the involved joint. This misleading perception of the disease by gouty patients is a major obstacle to the success of ULT [62], which, to be successful, must be applied chronically to get rid of the pathogenic crystals. Patients should therefore be fully informed about the pathophysiology of the disease including the link between chronic hyperuricemia and progressive deposition of the culprit crystals, the fact that crystals can be dissolved by prescribed drugs, leading to disappearance of disease features, and the obligation to take these drugs daily and chronically to insure the slow dissolution of crystals and prevent recurrences of the disease. Information about the existence of drug-induced flares at the onset of ULDs is also important as are the facts that they will disappear with time and can be prevented by appropriate prophylactic drugs. These drug-induced flares, when they are not understood nor appropriately prevented, probably explain, together with the perception of gout as an acute disease, why gout is the chronic disease

with the lowest adherence rate [63]. Health Professionals should also be convinced that gout is a chronic and serious disease -not only responsible for acute flares (which should not be the only focus of management) - that deserves that they spend time to inform the patients. Importance of genetic factors in the pathophysiology of the disease should also be kept in mind and challenges the widespread conception that gout is only a self-inflicted disease caused by food and alcohol misbehaviors, that would not deserve much attention. Adherence to long-term ULT has a central role in the success of gout management and cannot be obtained without careful, timely deliverance of key information to the patients. Previous recommendations from various rheumatology societies have previously emphasized this point [6, 8, 9], that has now been demonstrated by a large randomized trial [16].

The number of recommendations was voluntarily limited to 5, in order to provide short and easy-to-use guidelines, on the most important aspects of chronic management. Several drugs were left out of this set of recommendations. Uricases were not covered. Although they may be useful in refractory gout patients, they are either not available (Pegloticase), or not approved (Rasburicase) in France for the management of gout. Readers can find valuable recommendations on their use by the ACR or the EULAR [8]. Uricosurics were not covered either. Probenecid is the only uricosuric drug presently readily available in France, and is very seldom used, probably because it is reputed as being more difficult to use than xanthine oxidase inhibitors (XOIs), namely allopurinol and febuxostat. Urolithiasis is a contraindication and measures aimed at prevention of uric acid stones (abundant fluid intake, maintenance of the urinary pH above 6) are believed to be tedious and difficult to implement. In addition, probenecid interferes with the urinary excretion of many drugs, and these poorly known interactions restrain its use. We acknowledge that the addition of an uricosuric drug to a XOI is an efficacious strategy to attain the SU target in patients in whom XOIs are not sufficient, as shown by the recent development of lesinurad [64]. Yet lesinurad is not available in France, and requires uneasy renal function monitoring in the long run. In addition, the committee thought that patients refractory to XOIs are probably rare if the dosage of the XOI drug, in particular allopurinol, is

increased enough. The time when ULDs should be introduced was also not included in our recommendations. Even though ULDs have been traditionally recommended to be started at a distance from a flare to avoid worsening of the inflammation, recent studies have suggested that they could be started during a flare provided that an active anti-inflammatory treatment was maintained to control the flare and prevent its exacerbation [65].

A treat-to-uricemia target strategy (T2T) was strongly and unanimously recommended by the committee, in accordance with other Rheumatology societies [6, 8, 9, 66], despite the lack of a formal trial supporting its efficacy, as pointed out by the American College of Physician [10, 11]. The pathophysiology of the disease and double blind trials [16, 67] strongly support this T2T strategy, even though a true treat-to-target trial appears as most desirable to convince our American GP colleagues. We chose a SU target below 300 µmol/L (50mg/L) for all gout patients, considering that the target of 360 µmol/L provided slower depletion of MSU crystals [16, 68, 69], which would lead to slower clinical improvement, with the risk of discouraging the patient to continue ULDs. This target remains well above the low values of uricemia that have been suspected to associate with increased mortality or Parkinson's disease [70-72]. When a < 300 µmol/L SU target cannot be safely reached, values under 360 µmol/L can be accepted. The T2T strategy also decreases the risk of clinical inertia [13], meaning an insufficient dosage maintained on the long run, not allowing to reach SU target. Indeed both allopurinol and febuxostat, when slowly and safely titrated, lead almost all gout patients to target within few months [73].

Indication of ULDs was extended as compared to previous recommendations, given that the committee recommended to treat all gout patients, even from the first gout flare, provided that a firm diagnosis of gout has been made, therefore excluding patients with asymptomatic hyperuricemia or uncertain diagnosis. This can be taken as a step forward in simplifying the message with the aim to reduce the well-known gout under-treatment in France and elsewhere [13]. This recommendation relied on a consensual expert opinion based on the interpretation of available data

and was not based on evidence, no RCT being available on this matter. The task force unanimously agreed that the potential benefit of treating all patients with definite gout exceeded the risks inherent to ULT use if prescriptions were made appropriately to avoid allopurinol-induced SCARs.

The precise recommendation of when to use first-line allopurinol or febuxostat relying on renal function aims to provide clear guidance for physicians and to decrease the risk of SCARs related to ULTs. An important point is to increase the dosage of ULDs sufficiently to attain the desirable target. In France, allopurinol dosage is most frequently limited to 300 mg/d [12], a dose which is frequently too low to attain the SU target [26]. The maximum approved dosage of allopurinol in France is 900 mg/d in patients without CKD, allowing progressive increment of allopurinol dosage well above 300 mg/d, if necessary. Close patient follow-up during the ULD titration period can be facilitated by phone calls or internet exchanges to avoid repeated visits and to allow faster reach of the target SU. These strategies, that are used by many members of the recommendation committee, have not yet been formally tested but appear as promising.

The task force debated the place of HLA*B-5801 genotyping prior to allopurinol prescription, as this allele has been strongly associated with SCARs, especially in Han Chinese and South Asian populations. In French Caucasians, this allele is very rare and carried by only 50 % of patients who develop SCARs to allopurinol making genotyping unworthy [74]. The high negative predictive value of the absence of HLA*B5801 in South Asian populations makes pre-testing more interesting in these populations that include Vietnamese, who are numerous in France, especially in patients with inevitable risk factors such as renal failure. However, indications are rare, and genotyping is not reimbursed by the French National Insurance, so that this point was left out of the recommendations, for the sake of brevity.

Flare prophylaxis appears as very important as drug-induced flares frequently lead patients to stop the ULD treatment. In addition to progressive urate lowering, obtained by titration of ULDs [48], small doses of colchicine have been proved to prevent flares [49], and are the most common drug

prophylaxis used in France [75]. Several trials have now shown that low dose colchicine improved cardio-vascular outcome in the long run [76, 77], a supplementary reason to promote use in gouty patients who have a high risk of cardiovascular disease and death. However, even small doses can lead to serious side effects when colchicine is associated with drugs that interact with its pharmacodynamic or is prescribed in CKD patients. Colchicine should therefore be prescribed cautiously in these settings; the dose should be lowered and the patient should be informed of and monitored for toxicity. Muscular involvement should particularly be monitored, clinically and by periodic serum creatine kinase measurement in patients with renal failure, who can develop rhabdomyolysis, especially if they also take a statin [78, 79]. Although NSAIDs are largely used worldwide for flare prophylaxis, no RCT trial has proven their efficacy and their cardio/renal side effects have been emphasized, making them frequently unsuitable for gouty patient. No mention was made in our recommendations of the potential usefulness of small doses of corticosteroids, which have been mentioned in other guidelines [7], as they are not supported by any trial, and the clinical experience of our committee did not support their use. In contrast, steroids should be used early in the management of drug-induced flares in patients contraindicated for low dose colchicine and NSAIDs, and therefore left without prophylactic drug treatment. IL-1 blockers could also be used in those patients when steroids appear as hazardous (see part 1). Interleukin-1 inhibition has been shown to be effective for flare prophylaxis in one phase 2 trial but has not been approved in this indication [80].

Management of gout-associated comorbidities is emphasized in our last recommendation and aims at decreasing the risk of premature death associated with gout [81]. Smoking cessation, weight loss in the obese patient, and regular exercise should be encouraged to lower the cardiovascular risk. The effect of some drugs on SU should be taken into account in the management of comorbidities. Dyslipidemias should be treated by fenofibrate [56], or statins [57, 82] that will help decreasing SU level by their uricosuric properties. For hypertension management, thiazide diuretics and beta-blockers should be avoided as they increase uricemia [83]. Losartan and/or calcium channel blockers

should be preferred as they also lower SU levels [83, 84]. However, a pharmacodynamic interaction leading to increased colchicine serum level and toxicity should be kept in mind when colchicine and calcium channel blockers are co-prescribed [51]. For diabetes, insulin and insulin-secreting drugs such as sulfamides should be avoided as far as possible, because insulin increases tubular uric acid reabsorption [85, 86]. Metformin may induce beneficial weight loss and SU lowering [87]. It may also decrease the number of flares by inhibition of the mTOR pathway [88]. Among the new oral antidiabetic drugs, SGLT2 inhibitors appear as the most interesting as they decrease weight, cardiovascular disease and SU [89].

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References

[1] Dalbeth N, Merriman TR, Stamp LK. Gout. Lancet 2016;388(10055):2039-52.

[2] Bursill D, Taylor WJ, Terkeltaub R, Abhishek A, So AK, Vargas-Santos AB, et al. Gout, Hyperuricaemia and Crystal-Associated Disease Network (G-CAN) consensus statement regarding labels and definitions of disease states of gout. Ann Rheum Dis 2019;78(11):1592-600.

[3] Bardin T, Bouee S, Clerson P, Chales G, Flipo RM, Liote F, et al. Prevalence of Gout in the Adult Population of France. Arthritis Care Res (Hoboken) 2016;68(2):261-6.

[4] Richette P, Clerson P, Perissin L, Flipo RM, Bardin T. Revisiting comorbidities in gout: a cluster analysis. Ann Rheum Dis 2015;74(1):142-7.

[5] Richette P, Perez-Ruiz F, Doherty M, Jansen TL, Nuki G, Pascual E, et al. Improving cardiovascular and renal outcomes in gout: what should we target? Nat Rev Rheumatol 2014;10(11):654-61.

[6] Khanna D, Fitzgerald JD, Khanna PP, Bae S, Singh MK, Neogi T, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res (Hoboken) 2012;64(10):1431-46.

[7] Khanna D, Khanna PP, Fitzgerald JD, Singh MK, Bae S, Neogi T, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 2: therapy and antiinflammatory prophylaxis of acute gouty arthritis. Arthritis Care Res (Hoboken) 2012;64(10):1447-61.

[8] Richette P, Doherty M, Pascual E, Barskova V, Becce F, Castaneda-Sanabria J, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. Ann Rheum Dis 2017;76(1):29-42.

[9] Hui M, Carr A, Cameron S, Davenport G, Doherty M, Forrester H, et al. The British Society for Rheumatology Guideline for the Management of Gout. Rheumatology (Oxford) 2017.

[10] Qaseem A, Harris RP, Forciea MA, Clinical Guidelines Committee of the American College of P. Management of Acute and Recurrent Gout: A Clinical Practice Guideline From the American College of Physicians. Ann Intern Med 2017;166(1):58-68.

[11] Dalbeth N, Bardin T, Doherty M, Liote F, Richette P, Saag KG, et al. Discordant American College of Physicians and international rheumatology guidelines for gout management: consensus statement of the Gout, Hyperuricemia and Crystal-Associated Disease Network (G-CAN). Nat Rev Rheumatol 2017;13(9):561-8.

[12] Goossens J, Lancrenon S, Lanz S, Ea HK, Lambert C, Guggenbuhl P, 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(4):447-53.

[13] Maravic M, Hincapie N, Pilet S, Flipo RM, Liote F. Persistent clinical inertia in gout in 2014: An observational French longitudinal patient database study. Joint Bone Spine 2018;85(3):311-5.

[14] Pascart T, Norberciak L, Ea HK, Graf S, Guggenbuhl P, Liote F. Difficult-to-treat gout flares: eligibility for interleukin-1 inhibition in private practice is uncommon according to current EMA approval. Rheumatology (Oxford) 2019;58(12):2181-7.

[15] Latourte A, Pascart T, Chalès G, Coblentz-Baumann L, Cohen Solal A, Ea HK, et al. 2020 Recommendations from the French Society of Rheumatology for the management of gout. Part 1: management of acute flares. Joint Bone Spine 2020.

[16] Doherty M, Jenkins W, Richardson H, Sarmanova A, Abhishek A, Ashton D, et al. Efficacy and cost-effectiveness of nurse-led care involving education and engagement of patients and a treat-to-target urate-lowering strategy versus usual care for gout: a randomised controlled trial. Lancet 2018;392(10156):1403-12.

[17] Rees F, Jenkins W, Doherty M. Patients with gout adhere to curative treatment if informed appropriately: proof-of-concept observational study. Ann Rheum Dis 2013;72(6):826-30.

[18] Martinon F, Petrilli V, Mayor A, Tardivel A, Tschopp J. Gout-associated uric acid crystals activate the NALP3 inflammasome. Nature 2006;440(7081):237-41.
[19] Bursill D, Taylor WJ, Terkeltaub R, Kuwabara M, Merriman TR, Grainger R, et al. Gout, Hyperuricemia and Crystal-Associated Disease Network (G-CAN) consensus statement regarding labels and definitions for disease elements in gout. Arthritis Care Res (Hoboken) 2018.
[20] Bardin T. Hyperuricemia starts at 360 micromoles (6 mg/dL). Joint Bone Spine 2015;82(3):141-3.
[21] Abhishek A, Jenkins W, La-Crette J, Fernandes G, Doherty M. Long-term persistence and adherence on urate-lowering treatment can be maintained in primary care-5-year follow-up of a proof-of-concept study. Rheumatology (Oxford) 2017;56(4):529-33.
[22] Dalbeth N, Billington K, Doyle A, Frampton C, Tan P, Aati O, et al. Effects of Allopurinol Dose Escalation on Bone Erosion and Urate Volume in Gout: A Dual-Energy Computed Tomography Imaging Study Within a Randomized, Controlled Trial. Arthritis Rheumatol 2019;71(10):1739-46.
[23] Ellmann H, Bayat S, Araujo E, Manger B, Kleyer A, Cavallaro A, et al. Effects of conventional uric acid lowering therapy on monosodium urate crystal deposits. Arthritis Rheumatol 2019.
[24] Yin R, Li L, Zhang G, Cui Y, Zhang L, Zhang Q, et al. Rate of adherence to urate-lowering therapy among patients with gout: a systematic review and meta-analysis. BMJ Open 2018;8(4):e017542.
[25] Scheepers L, Burden AM, Arts ICW, Spaetgens B, Souverein P, de Vries F, et al. Medication adherence among gout patients initiated allopurinol: a retrospective cohort study in the Clinical Practice Research Datalink (CPRD). Rheumatology (Oxford) 2018;57(9):1641-50.
[26] Schumacher HR, Jr., Becker MA, Wortmann RL, Macdonald PA, Hunt B, Streit J, et al. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial. Arthritis Rheum 2008;59(11):1540-8.
[27] Bardin T, Richette P. Impact of comorbidities on gout and hyperuricaemia: an update on prevalence and treatment options. BMC Med 2017;15(1):123.
[28] Rai SK, Choi HK, Choi SHJ, Townsend AF, Shojania K, De Vera MA. Key barriers to gout care: a systematic review and thematic synthesis of qualitative studies. Rheumatology (Oxford) 2018.
[29] Serlachius A, Gamble G, House M, Vincent ZL, Knight J, Horne A, et al. Illness Perceptions and Mortality in Patients With Gout: A Prospective Observational Study. Arthritis Care Res (Hoboken) 2017;69(9):1444-8.
[30] Kuo CF, Grainge MJ, Mallen C, Zhang W, Doherty M. Comorbidities in patients with gout prior to and following diagnosis: case-control study. Ann Rheum Dis 2016;75(1):210-7.
[31] Choi HK, Curhan G. Soft drinks, fructose consumption, and the risk of gout in men: prospective cohort study. BMJ 2008;336(7639):309-12.
[32] Juraschek SP, White K, Tang O, Yeh HC, Cooper LA, Miller ER, 3rd. Effects of a Dietary Approach to Stop Hypertension (DASH) Diet Intervention on Serum Uric Acid in African Americans With Hypertension. Arthritis Care Res (Hoboken) 2018;70(10):1509-16.
[33] Perez-Ruiz F, Martinez-Indart L, Carmona L, Herrero-Beites AM, Pijoan JI, Krishnan E. Tophaceous gout and high level of hyperuricaemia are both associated with increased risk of mortality in patients with gout. Ann Rheum Dis 2014;73(1):177-82.
[34] Perez Ruiz F, Richette P, Stack AG, Karra Gurunath R, Garcia de Yebenes MJ, Carmona L. Failure to reach uric acid target of <0.36 mmol/L in hyperuricaemia of gout is associated with elevated total and cardiovascular mortality. RMD Open 2019;5(2):e001015.
[35] Pagidipati NJ, Clare RM, Keenan RT, Chiswell K, Roe MT, Hess CN. Association of Gout With Long-Term Cardiovascular Outcomes Among Patients With Obstructive Coronary Artery Disease. J Am Heart Assoc 2018;7(16):e009328.

[36] Pascart T, Grandjean A, Capon B, Legrand J, Namane N, Ducoulombier V, et al. Monosodium urate burden assessed with dual-energy computed tomography predicts the risk of flares in gout: a 12-month observational study : MSU burden and risk of gout flare. Arthritis Res Ther 2018;20(1):210.
[37] Dalbeth N, Nicolaou S, Baumgartner S, Hu J, Fung M, Choi HK. Presence of monosodium urate crystal deposition by dual-energy CT in patients with gout treated with allopurinol. Ann Rheum Dis 2018;77(3):364-70.
[38] Robinson PC, Dalbeth N, Donovan P. The Cost-effectiveness of Biannual Serum Urate (SU) Monitoring after Reaching Target in Gout: A Health Economic Analysis Comparing SU Monitoring. J Rheumatol 2018;45(5):697-704.
[39] Stamp LK, Day RO, Yun J. Allopurinol hypersensitivity: investigating the cause and minimizing the risk. Nat Rev Rheumatol 2016;12(4):235-42.
[40] Hande KR, Noone RM, Stone WJ. Severe allopurinol toxicity. Description and guidelines for prevention in patients with renal insufficiency. Am J Med 1984;76(1):47-56.
[41] Stamp LK, O'Donnell JL, Zhang M, James J, Frampton C, Barclay ML, et al. Using allopurinol above the dose based on creatinine clearance is effective and safe in patients with chronic gout, including those with renal impairment. Arthritis Rheum 2011;63(2):412-21.
[42] Juge PA, Truchetet ME, Pillebout E, Ottaviani S, Vigneau C, Loustau C, et al. Efficacy and safety of febuxostat in 73 gouty patients with stage 4/5 chronic kidney disease: A retrospective study of 10 centers. Joint Bone Spine 2017;84(5):595-8.
[43] Kim SH, Lee SY, Kim JM, Son CN. Renal safety and urate-lowering efficacy of febuxostat in gout patients with stage 4-5 chronic kidney disease not yet on dialysis. Korean J Intern Med 2019.
[44] White WB, Saag KG, Becker MA, Borer JS, Gorelick PB, Whelton A, et al. Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout. N Engl J Med 2018;378(13):1200-10.
[45] Ghang B, Ahn SM, Kim J, Kim YG, Lee CK, Yoo B. Discontinuing febuxostat might cause more deaths than continuing febuxostat: the untold story from the CARES trial. Rheumatology (Oxford) 2019.
[46] Stamp LK, Chapman PT, Barclay ML, Horne A, Frampton C, Tan P, et al. A randomised controlled trial of the efficacy and safety of allopurinol dose escalation to achieve target serum urate in people with gout. Ann Rheum Dis 2017;76(9):1522-8.
[47] Stamp LK, Chapman PT, Barclay M, Horne A, Frampton C, Tan P, et al. Allopurinol dose escalation to achieve serum urate below 6 mg/dL: an open-label extension study. Ann Rheum Dis 2017;76(12):2065-70.
[48] Yamanaka H, Tamaki S, Ide Y, Kim H, Inoue K, Sugimoto M, et al. Stepwise dose increase of febuxostat is comparable with colchicine prophylaxis for the prevention of gout flares during the initial phase of urate-lowering therapy: results from FORTUNE-1, a prospective, multicentre randomised study. Ann Rheum Dis 2018;77(2):270-6.
[49] Borstad GC, Bryant LR, Abel MP, Scroggie DA, Harris MD, Alloway JA. Colchicine for prophylaxis of acute flares when initiating allopurinol for chronic gouty arthritis. J Rheumatol 2004;31(12):2429-32.
[50] Montseny JJ, Meyrier A, Gherardi RK. Colchicine toxicity in patients with chronic renal failure. Nephrol Dial Transplant 1996;11(10):2055-8.
[51] Terkeltaub RA, Furst DE, Digiacinto JL, Kook KA, Davis MW. 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(8):2226-37.
[52] Pascart T, Richette P. Colchicine in Gout: An Update. Curr Pharm Des 2018;24(6):684-9.
[53] Larsson SC, Burgess S, Michaelsson K. Genetic association between adiposity and gout: a Mendelian randomization study. Rheumatology (Oxford) 2018;57(12):2145-8.
[54] Li X, Meng X, He Y, Spiliopoulou A, Timofeeva M, Wei WQ, et al. Genetically determined serum urate levels and cardiovascular and other diseases in UK Biobank cohort: A phenome-wide mendelian randomization study. PLoS Med 2019;16(10):e1002937.

[55] Hori T, Ouchi M, Otani N, Nohara M, Morita A, Otsuka Y, et al. The uricosuric effects of dihydropyridine calcium channel blockers in vivo using urate under-excretion animal models. J Pharmacol Sci 2018;136(4):196-202.
[56] Waldman B, Ansquer JC, Sullivan DR, Jenkins AJ, McGill N, Buizen L, et al. Effect of fenofibrate on uric acid and gout in type 2 diabetes: a post-hoc analysis of the randomised, controlled FIELD study. Lancet Diabetes Endocrinol 2018;6(4):310-8.
[57] Zhang T, Pope JE. Cardiovascular effects of urate-lowering therapies in patients with chronic gout: a systematic review and meta-analysis. Rheumatology (Oxford) 2017;56(7):1144-53.
[58] Stack AG, Johnson ME, Blak B, Klein A, Carpenter L, Morlock R, et al. Gout and the risk of advanced chronic kidney disease in the UK health system: a national cohort study. BMJ Open 2019;9(8):e031550.
[59] Scire CA, Manara M, Cimmino MA, Govoni M, Salaffi F, Punzi L, et al. Gout impacts on function and health-related quality of life beyond associated risk factors and medical conditions: results from the KING observational study of the Italian Society for Rheumatology (SIR). Arthritis Res Ther 2013;15(5):R101.
[60] Chandratre P, Mallen C, Richardson J, Muller S, Hider S, Rome K, et al. Health-related quality of life in gout in primary care: Baseline findings from a cohort study. Semin Arthritis Rheum 2018;48(1):61-9.
[61] Becker MA, Schumacher HR, Benjamin KL, Gorevic P, Greenwald M, Fessel J, et al. Quality of life and disability in patients with treatment-failure gout. J Rheumatol 2009;36(5):1041-8.
[62] Doherty M, Jansen TL, Nuki G, Pascual E, Perez-Ruiz F, Punzi L, et al. Gout: why is this curable disease so seldom cured? Ann Rheum Dis 2012;71(11):1765-70.
[63] Briesacher BA, Andrade SE, Fouayzi H, Chan KA. Comparison of drug adherence rates among patients with seven different medical conditions. Pharmacotherapy 2008;28(4):437-43.
[64] Bardin T, Keenan RT, Khanna PP, Kopicko J, Fung M, Bhakta N, et al. Lesinurad in combination with allopurinol: a randomised, double-blind, placebo-controlled study in patients with gout with inadequate response to standard of care (the multinational CLEAR 2 study). Ann Rheum Dis 2016.
[65] Hill EM, Sky K, Sit M, Collamer A, Higgs J. Does starting allopurinol prolong acute treated gout? A randomized clinical trial. J Clin Rheumatol 2015;21(3):120-5.
[66] Kiltz U, Smolen J, Bardin T, Cohen Solal A, Dalbeth N, Doherty M, et al. Treat-to-target (T2T) recommendations for gout. Ann Rheum Dis 2016;76(4):632-8.
[67] Dalbeth N, Saag KG, Palmer WE, Choi HK, Hunt B, MacDonald PA, et al. Effects of Febuxostat in Early Gout: A Randomized, Double-Blind, Placebo-Controlled Study. Arthritis Rheumatol 2017;69(12):2386-95.
[68] Perez-Ruiz F, Calabozo M, Pijoan JI, Herrero-Beites AM, Ruibal A. Effect of urate-lowering therapy on the velocity of size reduction of tophi in chronic gout. Arthritis Rheum 2002;47(4):356-60.
[69] Ebstein E, Forien M, Norkuviene E, Richette P, Mouterde G, Daien C, et al. Ultrasound evaluation in follow-up of urate-lowering therapy in gout: the USEFUL study. Rheumatology (Oxford) 2018.
[70] Weisskopf MG, O'Reilly E, Chen H, Schwarzschild MA, Ascherio A. Plasma urate and risk of Parkinson's disease. Am J Epidemiol 2007;166(5):561-7.
[71] Simon KC, Eberly S, Gao X, Oakes D, Tanner CM, Shoulson I, et al. Mendelian randomization of serum urate and parkinson disease progression. Ann Neurol 2014;76(6):862-8.
[72] Kia DA, Noyce AJ, White J, Speed D, Nicolas A, collaborators I, et al. Mendelian randomization study shows no causal relationship between circulating urate levels and Parkinson's disease. Ann Neurol 2018;84(2):191-9.
[73] Liote F, Choi H. Managing gout needs more than drugs: 'Il faut le savoir-faire, l'Art et la maniere'. Ann Rheum Dis 2013;72(6):791-3.

[74] Lonjou C, Borot N, Sekula P, Ledger N, Thomas L, Halevy S, et al. A European study of HLA-B in Stevens-Johnson syndrome and toxic epidermal necrolysis related to five high-risk drugs. Pharmacogenet Genomics 2008;18(2):99-107.
[75] 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(4):630-9.
[76] Solomon DH, Liu CC, Kuo IH, Zak A, Kim SC. Effects of colchicine on risk of cardiovascular events and mortality among patients with gout: a cohort study using electronic medical records linked with Medicare claims. Ann Rheum Dis 2016;75(9):1674-9.
[77] Crittenden DB, Lehmann RA, Schneck L, Keenan RT, Shah B, Greenberg JD, et al. Colchicine use is associated with decreased prevalence of myocardial infarction in patients with gout. J Rheumatol 2012;39(7):1458-64.
[78] Tufan A, Dede DS, Cavus S, Altintas ND, Iskit AB, Topeli A. Rhabdomyolysis in a patient treated with colchicine and atorvastatin. Ann Pharmacother 2006;40(7-8):1466-9.
[79] Davis MW, Wason S. Effect of steady-state atorvastatin on the pharmacokinetics of a single dose of colchicine in healthy adults under fasted conditions. Clin Drug Investig 2014;34(4):259-67.
[80] Schlesinger N, Mysler E, Lin HY, De Meulemeester M, Rovensky J, Arulmani U, et al. Canakinumab reduces the risk of acute gouty arthritis flares during initiation of allopurinol treatment: results of a double-blind, randomised study. Ann Rheum Dis 2011;70(7):1264-71.
[81] Fisher MC, Rai SK, Lu N, Zhang Y, Choi HK. The unclosing premature mortality gap in gout: a general population-based study. Ann Rheum Dis 2017;76(7):1289-94.
[82] Derosa G, Maffioli P, Reiner Z, Simental-Mendia LE, Sahebkar A. Impact of Statin Therapy on Plasma Uric Acid Concentrations: A Systematic Review and Meta-Analysis. Drugs 2016;76(9):947-56.
[83] Choi HK, Soriano LC, Zhang Y, Rodriguez LA. Antihypertensive drugs and risk of incident gout among patients with hypertension: population based case-control study. BMJ 2012;344:d8190.
[84] Hamada T, Ichida K, Hosoyamada M, Mizuta E, Yanagihara K, Sonoyama K, et al. Uricosuric action of losartan via the inhibition of urate transporter 1 (URAT 1) in hypertensive patients. Am J Hypertens 2008;21(10):1157-62.
[85] MacFarlane LA, Liu CC, Solomon DH. The effect of initiating pharmacologic insulin on serum uric acid levels in patients with diabetes: a matched cohort analysis. Semin Arthritis Rheum 2015;44(5):592-6.
[86] Toyoki D, Shibata S, Kuribayashi-Okuma E, Xu N, Ishizawa K, Hosoyamada M, et al. Insulin stimulates uric acid reabsorption via regulating urate transporter 1 and ATP-binding cassette subfamily G member 2. Am J Physiol Renal Physiol 2017;313(3):F826-F34.
[87] Barskova VG, Eliseev MS, Nasonov EL, Volkov AV, Tsapina TN, Zilov AV, et al. [Use of metformin (siofor) in patients with gout and insulin resistance (pilot 6-month results)]. Ter Arkh 2005;77(12):44-9.
[88] Vazirpanah N, Ottria A, van der Linden M, Wichers CGK, Schuiveling M, van Lochem E, et al. mTOR inhibition by metformin impacts monosodium urate crystal-induced inflammation and cell death in gout: a prelude to a new add-on therapy? Ann Rheum Dis 2019;78(5):663-71.
[89] Wang Y, Hu X, Liu X, Wang Z. An overview of the effect of sodium glucose cotransporter 2 inhibitor monotherapy on glycemic and other clinical laboratory parameters in type 2 diabetes patients. Ther Clin Risk Manag 2016;12:1113-31.

Table 1. Overarching principles and specific recommendations for the management of urate lowering therapy.

		Category of evidence	Strength of recommendation	Level of agreement (mean ± SD)
Overarching principles				
A	Information and education of the patient are essential for success of long-term management of gout.	1b	A	10.0 ± 0
B	The gout patient needs to know that flares are related to chronic monosodium urate (MSU) crystal deposits. The goal of the treatment is the permanent decrease of the serum urate level to obtain complete dissolution of these deposits, for clinical symptoms to disappear and to prevent chronic complications of gout.	2a, 4	B-D	9.77 ± 0.62
C	The treating physician needs to take the time to inform the patient about: 1. The importance of reaching the serum urate level target to allow for the dissolution of MSU crystals 2. The importance of the long-term adherence of urate lowering therapy 3. The risk of gout flares during the introduction of urate-lowering therapy 4. The cardiovascular, metabolic and renal risks associated with gout 5.The necessary adaptations of daily habits (avoid alcohol and sugar-sweetened beverage consumption, encourage regular physical activity and weight loss)	2a, 2c	B	9.54 ± 0.90
Specific recommendations				
1	A permanent urate-lowering therapy is indicated as soon as the diagnosis of gout is established.	4	D	9.75 ± 0.65
2	Serum urate level must be decreased below 360 µmol/L (60 mg/L) and if possible, below 300 µmol/L (50 mg/L) in all gout patients. Once the target is reached, treatment must be maintained, and serum urate levels must be monitored once or twice yearly.	2b, 3a	B-C	9.77 ± 0.45
3	Choice of urate lowering drugs: • When the eGFR is above 60 ml/min/1.73m2, first-line urate-lowering treatment is allopurinol. The starting dose of allopurinol is 50-100 mg per day, to be increased by steps of 50 to 100 mg every 2 to 4 weeks until the serum urate target is reached. • When the eGFR is 30 to 60ml/min/1.73m2, allopurinol use must be cautious and febuxostat can be considered an alternative. • When the eGFR is below 30 ml/min/1.73m2, allopurinol must be avoided and febuxostat should be preferred. • Febuxostat use must be cautious for patients with severe cardiovascular diseases.	1b, 4	A-D	9.08 ± 1.04
4	Prophylaxis of gout flares induced with the initiation of urate-lowering therapy: • Flares must be prevented as soon as urate-lowering therapy is started, with the association	1c	A	9.62 ± 0.79

	of a 0.5 to 1 mg daily dose of colchicine for at least 6 months in the absence of contraindications and by starting low and progressively increasing doses of the urate lowering drug.			
5	Gout comorbidities: • Cardiovascular risk factors and diseases, metabolic syndrome and chronic kidney disease must be screened and managed.	4	D	9.85 ± 0.58

Figure 1. Flow-chart of the systematic literature review informing the task force. RCT: randomized controlled trial, ULT: urate-lowering therapy.

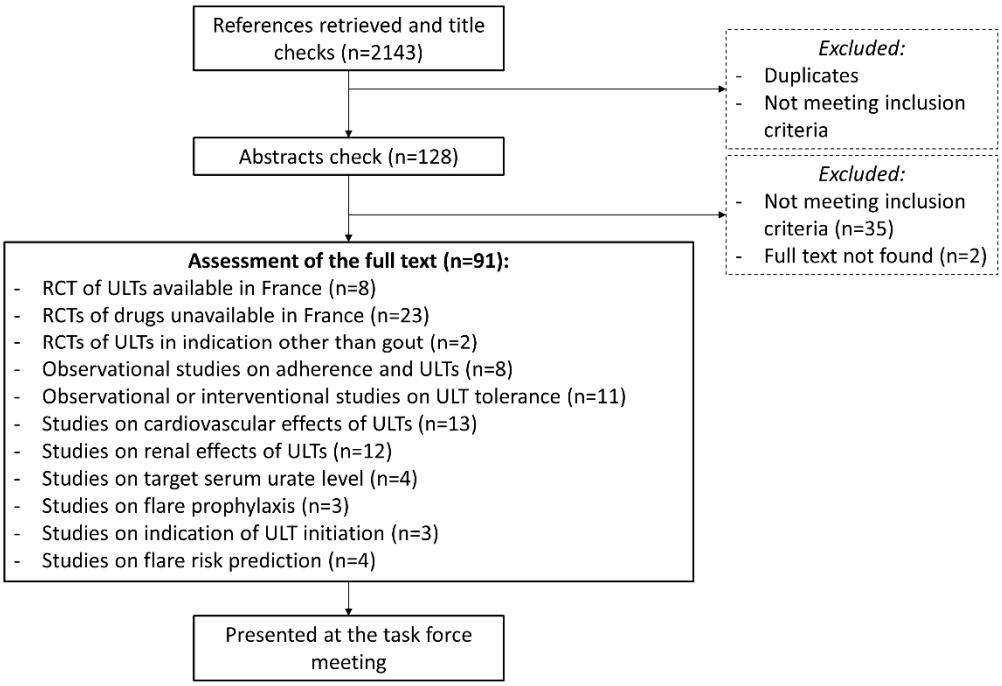

Figure 2. Management of urate-lowering therapy according to the Société Française de Rhumatologie.