

Treatment of hyperuricemia, gout and other crystalline arthritides

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SUMMARY

Gout is a very common joint disease which is due to chronic hyperuricemia and its related articular involvements. Yet it can be cured when appropriately managed. Comprehensive management of gout involves correct identification and addressing all causes of hyperuricemia, treating and preventing attacks of gouty inflammation (using colchicine NSAIDs, and/or steroids), and lowering serum urate (SUA) to an appropriate target level indefinitely. The ideal SUA target is, at a minimum, less than 6 mg/dL (60 mg/L or 360 µmol/L), or even less than 5 mg/dL in patients with tophi. The SUA target should remain at less than 6 mg/dL for long in all gout patients, especially until tophi have resolved. Patient education and adherence to therapy are key point to the optimal management of gout, aspects which are often neglected. Adherence can be monitored in part by continuing, regular assessment of the SUA level. More difficult cases of gout often need a combination of urate lowering therapy (ULT) for both refractory hyperuricemia and chronic tophaceous arthritis. Chronic tophaceous gouty arthropathy which do not respond adequately to optimized oral ULT might benefit from the use of pegloticase, when this is available in, for example, Italy and other European countries.

By contrast, in calcium pyrophosphate (CPP) crystal deposition disease (CPPD), as evidenced by pseudo gout attacks or chronic polyarthritis, similar anti-inflammatory strategies have been recommended, but there have as yet been no controlled trials. Of note, there is no treatment for the underlying metabolic disorders able to control the CPPD. Management of crystal-induced arthropathies (CIA) depends not only on clinical expression, namely acute attacks or chronic arthropathy, but also on the underlying metabolic disorder. We will mainly focus on gout as an archetype of CIA.

Key words: gout, hyperuricemia, diet, fructose, NSAID, steroid, ACTH, urate lowering therapy, allopurinol, febuxostat, uricosurics, IL-1 inhibitors, joint injection, calcium pyrophosphate crystal, chondrocalcinosis, basic calcium phosphate crystal.

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■ GOUT

General management

Gout management does not only concern the appropriate prescription of antiinflammatory drugs or urate lowering therapy (ULT). It is mandatory to consider patient education, or even the general practitioner's education.

In this chapter, we will summarize current management based upon the expert opinions set out in the 2006 EULAR (1, 2) and BSR (3) recommendations, in anticipation of the upcoming publication of the 2012 ACR recommendations for treatment of acute gout and hyperuricemia. Table I summarizes the recommended strategy for gout management.

Patient education

Is a key point since non-adherence in gout is high, even though patients experience painful attacks, compared to 'silent' diseases such as type 2 diabetes (DT2) and hypertension (HT). Indeed, a ULT medication possession ratio (MPR) of over 80%, a marker of adherence to treatment, is only achieved in 37% of patients with gout after one year, compared to 72% and 65% in HT and DT2, respectively (5). Gout patients should be provided with information on uric acid formation and its links to kidney dysfunction (genetic origin) and errors in diet. Information on gout pathogenesis, for example, gout attacks and crystal deposition disease on the one hand, and chronic hyperuricemia and urate storage on the

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Table 1 - Recommended strategy for gout management (1-4).

1. Identify cause(s) of chronic hyperuricemia, including drugs (thiazides), diet errors and lifestyle factors (low physical activity).
2. Identify comorbidities with respect to cardiovascular and renal risks.
3. Rule out rare increased cell turnover.
4. Identify family history of gout, hypertension, chronic kidney disease.
5. Diagnose and treat gout attacks as early as possible.
6. Assure prophylaxis of recurrent flares with appropriate measures (proper hydration, colchicine, other low dose anti-inflammatory agents).
7. Start and titrate urate lowering therapy at distance from last attacks, according to contraindications.
8. Monitor serum uric acid level in order to insure treat to target.
9. SUA level target is 360 $\mu\text{mol/l}$, or 6.0 mg/dl, or 60 mg/l in patients without tophus.
10. SUA level target is 300 $\mu\text{mol/l}$, or 5.0 mg/dl, or 50 mg/l in patients with tophus.
11. Monitor regularly (every 6 months) SUA level and creatinine clearance (MDRD formula).
12. Coordinate CV, obesity, diabetes and metabolic syndrome management with general practitioners, and *ad hoc* specialists.

other hand, should be regularly enforced. Also the 'treat to target' concept is a key point since regular serum uric acid (SUA) measurement will be of major importance in monitoring appropriate management. In addition, patients should be aware of risk factors for gout flares, and readily and rapidly use colchicine and/or NSAID when early symptoms occur.

Specific education on diet and lifestyle are pertinent to gout patients. After the first attack or diagnosis of gout, patients should be educated about the disease with respect to errors in diet. Table II provides a comprehensive survey of diet changes. This is not a major problem since only a few foods and drinks really have to be discontinued. Three beverages should be completely avoided: beers (including non-alcoholic beers), rich-fructose sodas such as regular colas, and spirits. The worst are the 'whisky-cola' or the 'Cuba Libre'! A moderate intake of calories from meat and seafood should be recommended. There are reasons to recommend low fat dairy products (uricosuric effect) (7), water (at least 5 units

Table 2 - Recommended diet changes in gout (1-3, 6).

1. Discontinue sugar (fructose-enriched) sweetened soft drinks and beverages.
2. Discontinue beer (with or without alcohol).
3. Discontinue liquors (whisky, vodka, etc).
4. Limit wine intake.
4. Limit meat intake.
5. Limit seafood intake in keeping with cardiovascular risks.
6. Recommend vegetable protein, legumes, nuts.
7. Consume low fat milk and dairy products (uricosuric effect).
8. Maintain coffee.
9. Recommend gradual reduced calorie intake and regular exercise in overweight and obese subjects.

(250 mL/unit) a day to reduce the risk of gout flare), coffee, vegetables and fruits; there is no increased risk from fruits or fruit juice (8).

Identification of causes of hyperuricemia

It is another key point since prevention can be provided at low risk and cost, and also because hyperuricemia and gout should be considered as independent risk factors for cardiovascular (CV) risk, including myocardial infraction (MI), cerebrovascular accident (CVA), and metabolic syndrome which encompasses DT2, dyslipidemia, and increased SUA level. These comorbidities should be systematically identified before choosing any gout medications, along with gastrointestinal diseases. Besides comorbidities, a systematic review should be made to identify hyperuricemic drugs (i.e. diuretics as antihypertensive agents or congestive heart failure drugs), errors in diet and lifestyle, and, more rarely, potential causes of increased cell turnover.

Elimination of non-essential drugs that trigger or maintain hyperuricemia should be systematically considered. Thiazides and loop diuretics prescribed for HT should be changed for other anti-HT drugs such as losartan or amlodipine, since they have uricosuric effects.

Treatment of gout attacks and pharmacological and non-pharmacological ULT

Patients urgently need treatment for gout attacks. Rapid analgesia and repeated inflammation are to be targeted. It is most

important to treat acute attacks as early as possible: we usually recommend that patients always have with them colchicine or NSAIDs so that they can start medication as soon as symptoms begin. There is an expected reduction in pain of 50% after 2-3 days with all available medications. Duration of treatment should be at least 10-15 days. Colchicine should be continued if ULT is considered.

It is important to rule out infectious arthritis since fever, chills, acute phase reactants and hyperleukocytosis can be present. Synovial fluid analysis should be performed in order to identify monosodium urate crystals, and bacteria by Gram staining followed by culture.

Choice and dose of antiinflammatory drugs depend upon patient comorbidities, including kidney function (9). It is now strongly recommended that serum creatinine level be measured and to calculate an estimated GFR by the MDRD formula; electronic devices or internet software are available.

Colchicine

Colchicine is considered the drug of choice in many countries, also in Europe, and each country has its own recommended dosage. A dose as low as 1.8 mg at Day 1 was recommended in the USA following the 'AGREE trial' (10), 1.5-2 mg at Day 1 is the recommended dose in Europe. In France, for example, 3 mg is the maximal daily dose, then a dose reduction down to 1 mg QD is recommended. When given after 12 h from the onset of the attack, the efficacy of colchicine might be reduced; this shows how important it is to start colchicine as early as possible. Drug interaction (DI) should be carefully controlled since, for example, a combination of statins and colchicine can trigger two severe adverse events (SAE), pancytopenia and rhabdomyolysis. Macrolides and pristinamycin are forbidden during colchicine therapy since they can trigger SAE as previously reported (11). Usual adverse events (AE) include nausea, vomiting or diarrhea; all gastrointestinal (GI) symptoms indicating overdosing. Diarrhea can be considered a severe adverse effect (SAE) in elderly pa-

tients at risk of dehydration followed by acute renal failure on top of chronic kidney disease (CKD). Colchicine dosing should be strictly enforced.

Non-steroidal antiinflammatory drugs (NSAID)

Any NSAID can be used to treat gout flare. Short life NSAIDs are safer since discontinuation might be necessary in case of AE. CV diseases and CKD are the comorbidities to consider when administering such drugs (12). Physicians should also consider age, past tolerance, risk of CV and GI AE, and cost. Recently, based upon a national data base survey in Denmark, patients with prior MI are at risk of death and re-infarction when given a course of NSAID as short as seven days and up to three months, after initial MI. Only naproxen was not associated with this increased and major CV risk (13). Duration of NSAID should be as short as possible. No difference was observed with available coxibs in terms of efficacy or CV safety compared with conventional NSAIDs (14).

Steroids and corticotrophin

Prednisone (or prednisolone) is an active anti-inflammatory agent in acute gout. It is as effective as NSAID (indomethacin 150 mg at Day 1 then 75 mg for 3 days, naproxen 1000 mg QD) at maximal dosage (9, 15, 16). A starting dose of 0.5 mg/kg prednisone should be considered, or 30-35 mg per day for five days. In some instances, a single dose of 100 mg IV methylprednisolone, or one injection of 40-60 mg IM triamcinolone acetonide could be indicated and allows administration to be controlled. Risk of increased tophi with long-term steroids in gout has been suggested (17). A few days of oral steroids could also be considered after parenteral administration. Overall duration should not exceed seven days to avoid AE (HT, DT2 disequilibrium, other).

A single injection of parenteral synthetic ACTH (corticotrophin) has also been used in a few patients and controlled trials are ongoing in some European countries.

IL-1 inhibitors

IL-1 β is the pivotal cytokine in gout flare. IL-1 inhibitors can be considered in patients with contraindications or experiencing side effects or refractory to respond to colchicine, NSAID and steroids. These patients can be considered as having 'difficult to treat' (DTT) gout. Actually they have much comorbidity, with moderate to severe CKD, high-dose furosemide for congestive heart failure (CHF), or previous SEA with the conventional drugs.

In short open series, off-label anakinra has been reported to provide rapid control of refractory or uncontrolled joint pain within 48 h in such DTT patients (16, 17). The standard regimen proposed empirically by So et al. is anakinra 100mg SC for three days (18), then the physician should consider treating on demand (recurrence of flare) or to maintain a low weekly dose of anakinra to prevent recurrence under appropriate ULT. Given the acceptable safety profile achieved in rheumatoid arthritis patients with a daily dose of anakinra, this supports its use in these fragile and elderly patients.

However, in our experience, even with a short half-life, we have had 2 out of 10 patients who developed severe infections (staphylococcal septic arthritis in an 80-year old man with CHF and CKD3; staphylococcal bilateral pulmonary abscesses with septicemia on a Port-a-Cath[®] catheter in a 40-year old woman with anorexia nervosa). Indeed, careful follow up and even survey for latent infection before anakinra administration should be considered. The risk-benefit ratio should also be discussed in patients with DT2.

Canakinumab, a humanized monoclonal antibody raised against IL-1 β , has been approved in cryopyrin-associated periodic syndrome (CAPS) (Ilaris[®]). It is administered at 150 mg SC for three months. Current dossiers with phases II and III studies (20, 21) are under evaluation at the European Medicines Agency (EMA) in the indication of DTT patients with gout and acute flares. It has a long half-life and might be of potential interest in treating patients with gout or in preventing flares.

However, some issues are still a subject of debate, in terms of tolerance, market access and cost.

Urate lowering therapy

The role of ULT is to reduce SUA level below the super saturation point, i.e. below 420 μ mol/L (70 mg/L). This concentration might be lower in distal and colder joints. It should be noted that a low percentage of gout attacks develops in some patients with levels between 60 and 70 mg/L (22). Thus, the SUA target to achieve is below 60 mg/L (6.0 mg/dL, 360 μ mol/L) (23) or even below 50 mg/L (5.0 mg/dL, 300 μ mol/L) in patients with tophi. The lower the level the faster the tophi will dissolve. Since gout is a storage disease, reduction of urates will need months or even years of ULT in patients with the most severe forms of gout.

Patients to be treated are severe patients including those having had at least two attacks, gout patients with tophi, clinical or radiological arthropathy, and urolithiasis. To date there is no recommendation for gout patients with subclinical tophi including those identified by ultrasound study. Additional issues are patients with organ transplantation, or with CKD.

Of note, to date hyperuricemia is not an indication for the use of ULT, but should rather lead to monitoring for and discontinuation of hyperuricemic drugs, controlling errors in the diet, and the use of lipid lowering drugs with uricosuric effects, such as fenofibrate or atorvastatin (24, 25).

First-line ULT

The choice of first-line ULT is a xanthine oxidase inhibitor (XOI), namely allopurinol or febuxostat (26). They are both effective in gout whatever the mechanism of hyperuricemia, including reduced renal excretion.

Allopurinol should be started at 100 mg QD and increased gradually depending upon SUA target. Allopurinol dosing should be adjusted to renal function by 50 or 100mg every 2-3 weeks according to regulations in force in each country. There is no rush to reduce SUA level below target; a slow,

steady reduction is more efficacious. A maximal allopurinol dosage is 800-900 mg in patients with normal GFR. There is no 'standard' dosage of 300 mg QD and even 400 or 450 mg QD might be sufficient to control SUA level.

By contrast, patients with impaired renal function might not be controlled with low doses and additional or alternative ULT could be needed. A major issue is the occurrence of skin rash or more severe skin reactions including DRESS or Lyell syndrome. In any case of rash, however slight, allopurinol should be definitively discontinued and the patient duly informed. Any reintroduction might lead to a severe hypersensitivity reaction and could be lethal.

Febuxostat (80 and 120 mg) is another XOI with a different structure from allopurinol. It can be used without adjustment in patients with GFR as low as 30 mL/min (26). In some instances it has been proposed as an alternative to allopurinol when this leads to intolerance, allergy or inefficacy. It has been considered as a second-line XOI after allopurinol given its availability, price, and safety issues (cardiovascular risk should be evaluated in an ongoing phase IV study) (27). In Europe, it is not recommended in patients with CHF and coronary heart disease.

Second-line ULT

Uricosurics are often considered as second-line ULT after failure of both XOI. Indeed, they inhibit URAT-1, one of the urate transporter at the basal membrane tubule, and show a real pathogenic mechanism of action. Available uricosurics in Europe depend on each country's formularies and regulations. As such probenecid (28), benzbromarone (29, 30) or sulfinpyrazone might be of value.

Uricosurics should be avoided in patients with a past history of uric acid urolithiasis. Patients with over 600 mg/24-h urine acid excretion should not be prescribed uricosurics. Benzbromarone should not be used in patients with liver impairment and abnormal transaminase levels since very rare liver cytolysis has been reported.

A combination of XOI and uricosurics is another possibility that has been promoted by Dutch and Spanish rheumatologists, with good results (28).

Prevention of flares

Gout attacks occur during the first months of ULT since MSU crystals are mobilized from intra-articular tophi. Patients should be clearly warned since they should not consider these flares to be a sign of treatment failure. Therefore, prevention is a key point to consider.

Prophylaxis with colchicine 1 mg daily should be started 2-3 weeks before initiating ULT. Low-dose NSAIDs (naproxen 125 mg BID, diclofenac 25 mg BID) might be an alternative, although mid-term tolerance is unknown. In some instances, a combination of low-dose colchicine and NSAID might be appropriate. In the future, IL-1 inhibitors might be of interest in DTT patients with comorbid conditions. Prevention measures should last at least six months in patients with febuxostat (according to European regulations) and can also be proposed for patients using allopurinol, or even as long as tophi are present (2, 3, 27).

Other measures

Management of comorbidities should be considered with primary care physicians and other specialists (cardiologists, nephrologists, endocrinologists). Specific attention should be paid to obesity and metabolic syndrome, and adjustment of an antihypertensive drug regimen.

■ CALCIUM PYROPHOSPHATE CRYSTAL DEPOSITION DISEASE

CPP crystal deposition disease was reviewed in 2011 by an *ad hoc* EULAR committee (31, 32). Several definitions have been renamed since the term chondrocalcinosis should be limited to radiological calcifications of hyaline cartilage and fibrocartilage. By contrast, acute synovitis is similar to gout attacks and was previously

named 'pseudogout'. Other conditions are chronic polyarthritis and CPPD, and osteoarthritis (OA) with CPPD.

General management of acute arthritis with CPP crystals

As mentioned for gout, comorbidities and age are key features to consider when treating patients with acute CPP arthritis. Local intra-articular steroid injection, after ruling out infection, might be valuable. Use of NSAIDs in elderly patients should be kept to a minimum.

Colchicine is also an alternative but should be started as early as possible since both drugs are less effective than in gout flares. Low-dose oral steroids can also be considered in some patients.

Chronic polyarthritis with CPPD

Some patients present with oligo- or polyarthritis and various DMARDs used in treating patients with rheumatoid arthritis have been evaluated in small open or controlled studies.

Hydroxychloroquine may provide some benefit in patients with chronic polyarthritis and reduce the number of flares. Low-dose weekly methotrexate has been disappointing since small open reports have suggested a potential therapeutic interest (31). At the last 2011 EULAR meeting, an ongoing controlled study suggested no efficacy compared to placebo in reducing the number of flares.

■ BASIC CALCIUM PHOSPHATE CRYSTAL ASSOCIATED JOINT INVOLVEMENT

Interestingly, BCP crystals are mainly involved in periarticular inflammation, and more rarely in triggering acute synovitis. In acute peri-arthritis or subacromial bursitis, physicians should consider several non-pharmacological and pharmacological measures: local ice pads, mild dose of prednisone for few days (e.g. 20 mg QD for 3-5 days) or full-dose NSAID to be adjusted to comorbidities, as discussed above.

Tendinitis will be managed with analgesics, NSAIDs, or periarticular joint steroid injections. Differences have been coined in terms of efficacy between 'blind' and ultrasound or X-ray guided injections (33). Rotator cuff rehabilitation with specific exercises in order to lower the humeral head might be enforced (34).

Of note, the Milwaukee shoulder syndrome is related to destructive arthropathy at the shoulder joint and more rarely at the knee joint. Large hemorrhagic effusion may occur and will rapidly require synovial fluid aspiration to provide relief, and steroid injection providing evidence of sterile effusion.

Shoulder prosthesis should be considered in some cases (standard shoulder replacement or reverse shoulder arthroplasty) according to muscle and tendon assessment (35).

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