Abstract

This review summarizes evidence relating to prophylaxis for gout flares after the initiation of urate-lowering therapy (ULT). We searched MEDLINE via PubMed for articles published in English from 1963 to 2013 using MeSH terms covering all aspects of prophylaxis for flares. Dispersion of monosodium urate crystals during the initial phase of deposit dissolution with ULT exposes the patient to an increased rate of acute flares that could contribute to poor treatment adherence. Slow titration of ULT might decrease the risk of flares. According to the most recent international recommendation, the two first-line options for prophylaxis are low-dose colchicine (0.5 mg once or twice a day) or low-dose NSAIDs such as naproxen 250 mg orally twice a day. They can be given for up to 6 months. If these drugs are contraindicated, not tolerated or ineffective, low-dose corticosteroids (prednisone or prednisolone) might be used. Recently, reports for four trials described the efficacy of canakinumab and rilonacept, two IL-1 inhibitors, for preventing flares during the initiation of allopurinol therapy. Prophylaxis for flares induced by ULT is an important consideration in gout management. Low-dose colchicine and low-dose NSAIDs are the recommended first-line therapies. Although no IL-1 blockers are approved as prophylactic treatment, this class of drug could become an interesting option for patients with gout with intolerance or contraindication to colchicine, NSAIDs or corticosteroids.

Key words: gout, flares, colchicine, non-steroidal anti-inflammatory drug, urate-lowering therapy, canakinumab, rilonacept, anakinra, corticosteroids.

Introduction

Gout is an inflammatory arthritis caused by deposition in the joints of monosodium urate (MSU) crystals that result from chronic hyperuricaemia. It is the most prevalent form of arthritis in adult males, and the worldwide incidence and prevalence are steadily increasing [1]. MSU crystal deposition in joints may be responsible for painful acute gout flares (GFs). Recurrent flares are associated with high socio-economic burden due to the frequent use of health care and impaired work productivity. In addition, gout not properly treated can cause joint destruction and permanent disability. Long-term treatment of gout aims to reduce the urate level below the limit of MSU solubility, thus dissolving MSU crystal deposits and leading to the disappearance of gout features. International guidelines recommend urate-lowering treatment (ULT) targets of <300–360 μmol/l (5–6 mg/dl) urate [2–4]. However, the dispersion of MSU crystals during the initial phase of deposit dissolution exposes the patient to an increased rate of acute flares that could contribute to poor treatment adherence [5]. Therefore prophylaxis for these ULT-induced flares is an important consideration in gout management. This article reviews available data on gout prophylaxis, with an emphasis on randomized controlled trials (RCTs) that examined the efficacy of prophylactic treatments after the initiation of ULT.

Data sources and search

We performed a comprehensive search of MEDLINE via PubMed for full-text English-language articles that were published from 1963 to 2013. The following search terms were used to retrieve key papers: gout, flares, arthritis, prophylaxis, prevention, uric acid-lowering therapy, urate-lowering therapy, allopurinol, febuxostat, pegloti-case, benz bromarone, probenecid, colchicine, NSAIDs, corticosteroids, canakinumab, anakinra, rilonacept and IL-1 blockers.
Eligibility criteria of RCTs

We then searched for all trials that examined the efficacy of prophylactic drugs during initiation of ULT by using the following search terms: gout, prophylaxis, prevention and randomized controlled trials (RCTs). Studies were eligible for inclusion if they were original articles of a randomized controlled design that included adults with gout and evaluated the prophylaxis of GFs following initiation of ULT. Studies were excluded if they were published in a non-English language, examined diseases other than gout, evaluated the treatment of acute GFs or their prophylaxis without initiating ULT or were a post hoc analysis of previously published data from RCTs. Other articles cited in this review were retrieved separately, either by checking references of relevant studies or by hand searching.

Result of the literature search on prophylactic drugs

We retrieved 44 articles for review, of which 17 did not specifically investigate gout. Thirteen of the 27 remaining articles did not have a randomized controlled design, were a post hoc analysis or were published in a non-English language, and were thus excluded. We excluded four additional articles that investigated either the treatment of acute GFs or their prophylaxis in the absence of ULT. Finally, five studies met our eligibility criteria. The main results of these RCTs are summarized in Table 1.

Pathogenesis of acute GFs

The pathogenesis of GFs mostly involves innate immune responses. Under certain conditions, such as with a rapid decrease of urate levels induced by ULT, the presence of free fatty acids after food intake or alcohol consumption [10, 11], or with bacterial lipopolysaccharides during an infection [12], MSU crystals can promote acute inflammation in joints. Mechanisms of this crystal-induced inflammation involve complement activation, but also a direct interaction of MSU crystals with neutrophils and macrophages, presumably via membrane phospholipids or Toll-like receptors [13]. Recently IL-1β was found to play a crucial role in MSU crystal-induced inflammation, through activation by crystals of the NOD-like receptor family, pyrin domain-containing 3 (NLRP3) inflammasome [14]. This cytoplasmic protein complex, when activated, leads to the cleavage and activation of caspase-1, which converts pro-IL-1β to its active form, IL-1β [15].

Colchicine is one of the most frequently used drugs for treating acute gout. It limits both the initiation and amplification of joint inflammation by modulating chemokine production and inhibiting neutrophils and endothelial cell adhesion molecules [16, 17]. Both the European League Against Rheumatism (EULAR) [2] and ACR [18] recommendations propose colchicine among the first-line drugs for pharmacological management of acute gout. Other options are NSAIDs or corticosteroids. More recently, IL-1 inhibitors, known to be effective in managing autoinflammatory diseases [19], have demonstrated efficacy in the treatment of acute GFs [20–22].

Colchicine, NSAIDs or corticosteroids, which are indicated for the treatment of acute GFs, may also be used for prophylaxis for GFs during the initiation of ULT, with low dosages (e.g. colchicine 0.5 mg once or twice a day), and given long term (i.e. up to 6 months), according to the individual risk of flares assessment.

GFs following ULT initiation

We lack robust data on the prevalence of GFs induced by ULT. Placebo arms from studies conducted with IL-1 blockers and colchicine gave important information on both flares triggered by ULT and their prophylaxis. In three recent placebo-controlled trials evaluating rilonacept, an IL-1 blocker, for preventing acute GFs during the initiation of allopurinol 300 mg/day, the proportion of patients in the placebo arm reporting at least one GF after 16 weeks of ULT ranged from 46.8% to 56.1% [7, 8, 23]. In another randomized, placebo-controlled trial assessing whether colchicine administration could reduce the frequency of flares during the initiation of allopurinol, this proportion reached 77% at 6 months for patients who received the placebo [9], even though a titration of allopurinol was performed.

Prophylactic treatment can decrease the rate of GFs triggered by the initiation of ULT but does not totally prevent the occurrence of flares, in particular with a sharp decrease in urate levels [24]. Studies of pegloticase and febuxostat have provided additional data on the rate of flares in patients treated with these powerful ULTs when given without slow upward titration. In two recent placebo-controlled trials evaluating pegloticase, known for markedly lowering urate levels, despite patients receiving colchicine 0.6 mg once or twice daily or an NSAID, the rate of GFs in the first 3 months exceeded 75% in both pegloticase groups (8 mg i.v. biweekly or monthly) as compared with 53% in the placebo group (P=0.02 and 0.002, respectively) [25].

In the first trial comparing febuxostat to allopurinol [26], the prophylaxis for acute GFs was administered for the first 8 weeks (250 mg of naproxen twice daily or 0.6 mg of colchicine once daily). After cessation of the prophylactic treatment, the frequency of GFs increased markedly. Overall, ~60% of patients experienced acute attacks during the analysed period of 1 year. This proportion was significantly higher with 120 mg febuxostat than 80 mg febuxostat or allopurinol. Furthermore, GFs was one of the most frequent reasons given for study discontinuation.

Thus prevention of GFs in the initial phase of ULT is a core aspect of the management of gout and should always be considered, in particular for those ULTs that drop urate rapidly, because such prevention might promote adherence to ULT.
Prophylactic treatments: current recommendations (EULAR, ACR)

Adherence to treatment is a key issue in the management of chronic gout, because once prescribed, ULT should remain for life. Unfortunately, non-adherence among patients with gout who start ULT is common [27]. This adherence may be compromised both by GFs triggered after ULT initiation and by the practice of delaying the introduction of ULT a few weeks after resolution of a flare. Indeed, the latter tends to promote the idea that no additional treatment is needed once an acute attack has resolved. In contrast to EULAR recommendations [2, 28], ACR guidelines recommend that ULT be started during an attack, if anti-inflammatory treatment has been introduced beforehand [3]. This strategy was supported by a recent RCT showing no difference in pain, recurrent flares or inflammatory markers with allopurinol initiated during an acute GF as compared with a 10-day delay in initiation [29].

To prevent GFs, international recommendations [2, 18] suggest that pharmacological anti-inflammatory prophylaxis be systematically considered with ULT at its initiation. Of note, a recent study found that following patient education and with slow upward titration of ULT, mostly allopurinol, many patients chose not to take prophylaxis and did not experience a significantly greater flare rate [30]. These data suggest that slow titration could be a core aspect of the management of ULT in order to decrease the risk of flares. However, due to the lack of a control group, further specific studies to assess the impact of titration on the incidence of flares are required.

The best duration for the prophylactic treatment is unknown and in the individual patient might depend on the severity of the crystal load, the velocity by which urate levels are lowered and the presence or not of factors known to trigger acute attacks. Data from pivotal trials conducted with febuxostat [26, 31, 32] have shown substantial rates of acute GFs in the first 6 months. Therefore

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ULT: urate-lowering therapy.
prophylaxis for 6 months or until resolution of tophi is recommended by the ACR guidelines [18]. A shorter duration, 3 months, may be proposed after achieving the target urate level for patients without tophi detected on physical examination [18]. According to the most recent recommendation [18], the two first-line options are low-dose colchicine (0.5 mg once or twice a day) and low-dose NSAIDs (such as naproxen 250 mg orally twice a day). If these drugs are contraindicated, not tolerated or ineffective, low-dose corticosteroids (prednisone or prednisolone) may be used.

**Colchicine**

The first placebo-controlled trial that evaluated the efficacy of colchicine as a prophylactic treatment randomized 52 patients beginning treatment with probenecid (500 mg three times daily) [33]. In this trial, colchicine 0.5 mg was administered daily for 6 months. The annual rates of GFs were 2.3 in the colchicine group and 6.0 in the placebo group (P < 0.05). Subsequently, in 2004, Borstad et al. [9] compared colchicine 0.6 mg twice a day to placebo for prophylaxis for GFs during the initiation of allopurinol in 43 patients. Allopurinol was initiated at 100 mg/day and then its dosage was increased in 100 mg increments until a serum urate level <6.5 mg/dl was attained. After 6 months, 33% of the patients who received colchicine experienced GFs, compared with 77% in the placebo group (P = 0.008). From this study it was computed that the number needed to treat was 2 (95% CI 1, 6), suggesting that colchicine would prevent one in two patients from experiencing a GF [9]. In both trials, tolerance of colchicine was good, except for a significantly higher rate of gastrointestinal adverse events, in particular diarrhoea.

In 2010, Wortmann et al. [34] reanalysed data on GFs from three phase 3 RCTs of febuxostat [Febuxostat versus Allopurinol Controlled Trial (FACT) [26], Allopurinol and Placebo-Controlled, Efficacy Study of Febuxostat (APEX) [31] and CONFIRMS [32]). In these studies, >4000 patients received colchicine 0.6 mg daily or naproxen 250 mg twice a day as prophylaxis during the initiation of ULT. In the FACT and APEX trials, in which colchicine or naproxen was given for 8 weeks, the prevalence of GFs was markedly increased after the cessation of prophylaxis. In contrast, in the CONFIRMS trial, in which the prophylaxis was maintained for the entire duration of the study (6 months), GFs requiring treatment occurred in 10–15% of subjects in all treatment groups during each of the first 2 months of treatment and then decreased slowly over the remainder of the trial.

These data indicate that prophylaxis with febuxostat should be given for at least 8 weeks, for a total duration of 3–6 months, depending on both estimated crystal load and the risk of adverse events with the prophylactic drug.

In the FACT and APEX trials, adverse event rates were higher with colchicine than naproxen (55.1% vs 44.3%, respectively, P < 0.001), with especially more diarrhoea events in patients receiving colchicine. Thus low-dose oral colchicine reduces the rate of GFs after the initiation of ULT, but its safety in the long-term, especially in patients with frequent co-morbidities and multiple medications, deserves some consideration. Indeed, colchicine has a narrow therapeutic toxicity window, with important variability in tolerance among subjects. In 2011, Terkeltaub et al. [35] performed a large pharmacokinetic study and demonstrated multiple drug interactions with colchicine. In case of concomitant therapy with a strong P-glycoprotein inhibitor, such as ciclosporin, or a cytochrome P450 3A4 inhibitor, such as clarithromycin, ketoconazole or ritonavir, the dosage of colchicine should be lowered or the interval between doses should be increased, with tight monitoring of adverse events.

The dosage should also be reduced or dosing intervals increased for patients with chronic kidney disease, a condition often encountered in patients with gout [36, 37].

**NSAIDs**

Although low-dose NSAIDs are sometimes used as an alternative to colchicine in daily practice, evidence from randomized trials on their efficacy as prophylactic treatment is scarce. Two trials of 156 patients compared aza-propazone, an NSAID with uricosuric effects (600 mg twice daily) and allopurinol [38, 39]. Both drugs equally decreased urate levels. However, aza-propazone had additional prophylactic benefit against acute attacks but a poorer safety profile, with increased incidence of gastrointestinal adverse events.

As noted previously, the efficacy of low-dose NSAIDs as prophylaxis for GFs was also suggested in the phase 3 trials of febuxostat [34]. Considering all these data, the ACR recommended as a first-line prophylactic low-dose colchicine or naproxen 250 mg twice daily combined with a proton pump inhibitor, if indicated [18].

Of note, prescription of long-term NSAIDs, even at low dosages, in patients with gout requires carefully weighing the benefit-risk balance because of the cardiovascular, renal and gastrointestinal side effects of this class of drug [40, 41].

**Corticosteroids**

Oral corticosteroids are a recommended alternative for GFs for patients with contraindication to colchicine and NSAIDs [18]. This recommendation is supported by data from two RCTs [42, 43]. The most recent compared prednisolone 35 mg/day and naproxen 500 mg twice daily to treat acute gout, and showed equivalence for both efficacy and safety [43].

In contrast, no trial has specifically evaluated low-dose steroids (<10 mg equivalent prednisone/day) for prophylaxis for GFs. Low-dose prednisolone or prednisone is therefore recommended as second-line prophylactic treatment for patients with contraindications or intolerance to both NSAIDs and colchicine [18]. Because long-term use of corticosteroids can lead to several side effects, and in particular worsening of diabetes, the risk–benefit ratio should be evaluated regularly once treatment has begun.
IL-1 blockers

Recently, reports from four trials described the efficacy of two IL-1 inhibitors for the prevention of GFs during the initiation of ULT [6–8, 23]. The first trial investigated canakinumab, a fully human monoclonal antibody targeting IL-1β administered by s.c. injections. The other three studied rilonacept, also known as IL-1 Trap, a soluble receptor fusion protein binding both IL-1α and IL-1β, which is also administered subcutaneously.

Canakinumab has been approved by the European Medicines Agency for the symptomatic treatment of frequent acute GFs in patients in whom NSAIDs and colchicine are contraindicated, are not tolerated or do not provide an adequate response and in whom repeated courses of corticosteroids are not appropriate. The agent is not approved for prophylaxis for GFs. Of note, the US Food and Drug Administration has not approved canakinumab for either prophylaxis or the treatment of flares, mainly because of safety concerns.

In a phase 2 trial, Schlesinger et al. [6] compared six different doses of canakinumab and colchicine, 0.5 mg/day, in 432 patients beginning treatment with allopurinol. At 16 weeks the mean number of flares per patient was 0.23 with high doses of canakinumab (100 and 300 mg) and 0.75 with colchicine, with an estimated difference from colchicine treatment of –0.52 (P < 0.05). A post hoc analysis showed a significant decrease in the mean number of flares per patient for all canakinumab doses >50 mg vs colchicine. No evidence for a dose response for canakinumab was seen. The similarity was observed in each group, but more infections were observed in the canakinumab groups. Infectious adverse events were reported in 18% of patients receiving canakinumab and 12% of patients receiving colchicine. Canakinumab should not be administered during an active infection and physicians should exercise caution when administering it to patients with underlying conditions that may predispose them to infections. Other side effects reported with canakinumab are neutropenia and injection site reactions.

Three trials compared rilonacept with placebo for preventing GFs during the initiation of allopurinol 300 mg/day. In each trial a loading dose of rilonacept was initially administered, which was twice the dose administered weekly thereafter. In the phase 2 trial [7], 83 patients were randomized to receive rilonacept 160 mg/week or a placebo. The mean number of flares per patient at week 12 was significantly lower in the rilonacept than the placebo group (0.15 vs 0.79, P = 0.001). This beneficial effect occurred early and was maintained throughout the trial. Interestingly, no relapse was observed after the cessation of prophylaxis, and more patients in the rilonacept than the placebo group completed the evaluation period (98% vs 79%, P = 0.015). The rate of adverse events was similar between groups.

Two phase 3 trials compared two doses of rilonacept, 80 and 160 mg/week, with placebo in patients who received allopurinol. In both studies the treatment was administered for 16 weeks and the primary outcome was the number of flares per patient through week 16. In the first trial [23], of 241 patients, the mean number of flares per patient was significantly reduced in both rilonacept groups [1.06 in the placebo group vs 0.29 with rilonacept 80 mg and 0.21 with 160 mg (both P < 0.001)]. In the second trial [8], the mean number of flares per patient was reduced by 71.3% and 72.6% with rilonacept 80 and 160 mg, respectively (both P < 0.001). In these studies, the rate of adverse events was similar between groups, except for a higher risk of reaction at the injection site with rilonacept [8, 23]. In the second trial, 24% and 29% of patients developed anti-rilonacept antibodies in the 80 and 160 mg groups, respectively. The positivity of these antibodies was associated with higher injection site reaction rates [8]. The other most frequently reported adverse events were upper respiratory tract infection (including influenza viral infections) and headache. Rilonacept is not approved as prophylactic treatment for acute gout.

Overall, IL-1 blockers seem to have a relatively good safety profile for short-term use and showed satisfactory efficacy in the prophylaxis of acute GFs. They could be good candidates as alternative therapy to colchicine, NSAIDs or corticosteroids in situations of contraindication or intolerance to these drugs. Their cost and their putative infectious adverse events [44] preclude their use as a first-line prophylactic option.

Conclusions

Considering prophylaxis for acute GFs is critical in the management of gout because it may help to enhance adherence to ULT, which can cure gout, if taken appropriately. The currently recommended drugs [2, 18] for prophylaxis are those used to treat acute gout, but at a lower dosage. The available therapeutic options comprise colchicine, NSAIDs and oral corticosteroids. We lack data comparing their efficacy. Therefore the choice of drug should be based on tolerance, the presence of co-morbidities and other medications taken by the patient. In the near future, IL-1 blockers may be added to this armamentarium. Slow upward titration of ULT, when feasible, is a key aspect of the management of gout that allows for a decreased risk of flares.

Rheumatology key messages

- The two first-line options for prophylaxis in gout are low-dose colchicine and low-dose NSAIDs.
- The choice for prophylactic treatment of gout depends on co-morbidities, tolerance and coprescriptions.
- IL-1 blockers could become an option for gout patients with contraindications to colchicine, NSAIDs or corticosteroids.

Funding: This work was supported by the Association Rhumatisme et Travail (Hôpital Lariboisière, Paris, France).
Disclosure statement: P.R. received honoraria from AstraZeneca, Ipsen, Menarini, Novartis, Savient and Sobi. T.B. has received honoraria for consultancies from Novartis, Ipsen, Menarini, Savient, AstraZeneca and Sobi and has received honoraria for talks from Savient, Menarini and Ipsen. The other author has declared no conflicts of interest.

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