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Original Article

Prophylaxis on gout flares after the initiation of urate-lowering therapy: a retrospective research

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Abstract: The objective of this study was to evaluate the efficacy and safety associated with treatment available to prevent an acute attack of gout when initiating a urate-lowering therapy (ULT). We retrospectively reviewed patients who were diagnosed with gout and treated with ULT during the period from January 2000 to January 2014. They were divided into three groups, 75 patients without prophylaxis treatment, 103 patients treated with etoricoxib, and 129 patients with colchicine treatment. Both demographic and clinical characteristics associated with gout were analyzed. At baseline, demographic and clinical characteristics were generally similar in three groups. SU target level was achieved in 49.3% of the patients without prophylaxis treatment, 66.4% in the etoricoxib group and 65.1% in colchicine group, respectively. During the first 16 weeks, patients without prophylaxis treatment exhibited higher flare rates than patients in other two groups. However, no statistically significant difference was observed between patients in etoricoxib group and colchicine group. In the 16-24 weeks, the proportion of patients who reported flares were all decreased similarly in three groups. The mean number of acute gout flares per patient and gout flare days per patient was significantly higher in patients without prophylaxis treatment than patients in other groups. The mean number of acute gout flares was lower (4.2±2.3 vs 3.2±1.8) in patients with etoricoxib treatment than that in patients with colchicine treatment. Gout flare days per patient were significantly higher in patients without prophylaxis treatment. Compared to colchicine group, gout flare days per patient in etoricoxib were lower (1.2±0.5 vs 2.6±0.6). In term of AEs, patients receiving colchicine had higher rates of gastrointestinal AEs than those who received etoricoxib. In summary, our survey revealed that etoricoxib was more effective and safe than colchicine in preventing acute attack during ULT.

Keywords: Gout, etoricoxib, colchicine

Introduction

Gouty arthritis is mediated by monosodium urate monohydrate crystal deposition in and around the joint space due to hyperuricemia. The clinical feature of gout is recurrent acute inflammatory flares (acute gout flares) that result in debilitating joint pain and swelling [1]. The rate of gout has been increasing year by year [2]. At present, gout affects about 150 million people in China. Gout has been considered as a significant public health problem [3].

The goal of long-term treatment of gout is to decrease urate crystal deposition, which requires reducing the level of serum urate (SU) [4]. A 'treat to serum urate target' approach has been recommended in many gout treatment guidelines. These guidelines recommended that SU should be lowered to <6.0 mg/dl in patients with chronic gout and <5.0 mg/dl in patients with tophi [5, 6]. Paradoxically, initiation of urate lowering therapy (ULT) can induce a gout attack, likely as a result of remodeling of crystal deposits during dissolution. Acute gout flares are known to occur as a result of the initiation of ULT and effective reduction of SU. In fact, the greater the reduction in SU is, the more likely a flare will occur.

In order to decrease the high rate of gout attacks early in ULT, pharmacologic anti-inflammatory prophylaxis is recommended when initiating ULT. In 2012, the American College of

Rheumatology (ACR) guidelines offered a series of recommendations about prophylaxis during initiation of ULT. The guidelines recommended, as first-line prophylactic agents, the use of either low-dose colchicine or Non-steroidal anti-inflammatory drugs (NSAID). If neither of these two drugs is considered appropriate, low-dose prednisone can be considered. However, the recommendations for selection of a drug provide the clinician with considerable flexibility. In addition, the guidelines offer another important recommendation about the appropriate duration of anti-inflammatory prophylaxis. Prophylaxis should be continued for 6 months after initiation of ULT. In patients without tophi, prophylaxis may be stopped 3 months after achieving the target SU level. In patients where tophi had been present but resolved, prophylaxis should be continued for 6 months after achieving the target SU level. However, the recommendations encourages carefully evaluating the need for such therapy given the risks of prolonged steroid use [7].

There are no data on the efficacy and safety associated with treatment available to prevent an acute attack of gout when initiating ULT with respect to gout in China. We investigated these aspects using a retrospective cohort design.

Patients and methods

Patients

We retrospectively examined data on 307 patients who were diagnosed with gout and treated with a hypouricemic agent during the period from January 2000 to January 2014 in the outpatient clinics and ward at the Department of Rheumatology, The First Affiliated Hospital of Liaoning Medical University. Approval was obtained from an independent ethics committee.

The inclusion criteria for our study were as follows: patients had to have previously met ACR criteria for the classification of acute arthritis of primary gout, based on clinical features and/or demonstration of MSU crystals in joint fluid. In addition, patients were given the choice to insist on using ULT and obtaining follow-up care.

Based on prophylaxis, patients were divided into three groups, 75 patients without prophylaxis, 103 patients in etoricoxib group and 129 patients in colchicine group.

Measurements

For the purposes of descriptive analyses, the following data were recorded: age, sex, body mass index, duration of gout, laboratory analysis including mean serum uric acid, allopurinol dose, SU target were conducted at every outpatient visit.

In order to evaluate the efficacy of anti-inflammatory prophylaxis, we compared the proportion of patients who reported flares, mean number of gout flares per patient and the duration of the flare per patient.

A gout flare was defined as an incidence with three or more of the following criteria: any patient-reported warm joint(s), any patient-reported swollen joint(s), patient-reported pain (>3) at rest, on a scale of 0-10, and a flare reported by a patient or directly diagnosed by a physician.

Tolerability analysis: safety and tolerability were evaluated based on the incidence of adverse events (AEs) up to and including the safety follow up visit.

Statistical analysis

Statistical analysis was carried out using the Statistical Package for the Social Sciences (version 19.0; SPSS, Inc., Chicago, IL, USA). Means with standard deviations (SD) and percentages were used to describe the clinical characteristics of participants.

Analysis of variance was used to determine statistically significant differences between the two groups in baseline age, body mass index (BMI), SU, and number of years with gout. T-tests and Chi square analysis was used to compare groups of patients exhibiting target SU levels and frequency of acute gout attacks. A significance level of 0.05 was used.

Results

Demographic and clinical characteristics

Demographic and clinical characteristics were generally similar in three groups. Patients in the without prophylaxis group were predominantly

Table 1. Characteristics of patients in each group

Parameters	Without prophylaxis group	Etoricoxib group	Colchicine group
Gender *n* (%)			
Male	75 (98.6%)	123 (95.9%)	109 (97.1%)
Female	2 (1.4%)	5 (4.1%)	3 (2.9%)
Age (years)			
Mean ± SD	43.1±2.5	47.9±3.2	44.9±3.8
BMI (kg/m^2)			
Mean ± SD	29.2±4.1	30.2±3.8	31.5±1.4
Duration of gout (years)			
Mean ± SD	4.8±1.7	5.1±1.3	5.0±2.3
Mean serum uric acid (mg/dL)			
Mean ± SD	7.2±0.8	7.8±1.4	7.5±1.3
Allopurinol dose, mg/day			
Mean ± SD	230±55.6	220±67.2	230±45.9
SU target *n* (%)	77 (49.3%)	85 (66.4%)*	73 (65.1%)*

*Compared to without prophylaxis group, P<0.05. Analysis of variance was used to determine statistically significant differences between the two groups in baseline age, BMI, SU, and number of years with gout. T-tests and Chi square analysis was used to compare groups of patients exhibiting target SU levels.

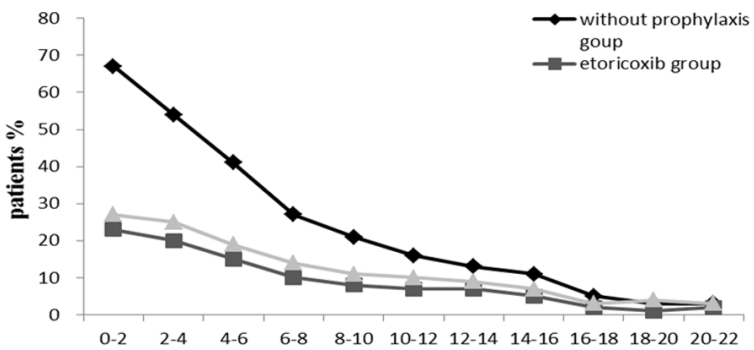

Figure 1. Proportion of patients reporting gout flares in each group.

male (98.6%), and had a mean age of 43.1±2.5 years and a BMI of 29.2±4.1 kg/m^2. The mean duration of gout was 4.8±1.7 years. Patients in etoricoxib group were predominantly male (95.9%), and exhibited a mean age of 47.9±3.2 years and a BMI of 30.2±3.8. The mean duration of gout was 5.1±1.3 years. Patients in colchicine group were predominantly male (97.1%), and exhibited a mean age of 44.9±3.8 years and a BMI of 31.5±1.4. The mean duration of gout was 5.0±2.3 years (**Table 1**).

ULT

At baseline, there was no significant difference in mean SU and the dosage of allopurinol in three groups. Serum urate levels <6.0 mg/dL (the SU target level) were achieved by 49.3% of the patients in without prophylaxis group, 66.4% in the etoricoxib group and 65.1% in the colchicine group, respectively. The percentage of the treatment-to-target ratio in without prophylaxis group was lower than the other groups (P<0.05) (**Table 1**).

Flare rates

The proportion of patients who reported flares were comparable among patients. During the first 16 weeks, patients in without prophylaxis group exhibited higher flare rates than those in other groups. However, no statistically significant difference was observed between in etoricoxib group and colchicine group. In the 16-24 weeks, the proportion of patients who reported flares were all decreased in three groups, what's more, the values were generally similar in three groups (**Figure 1**).

The mean number of acute gout flares per patient and gout flare days per patient was significantly higher in without prophylaxis group than other groups. Compared to colchicine group, the mean number of acute gout flares per patient in etoricoxib group was lower (4.2±2.3 vs 3.2±1.8) (P<0.05). Gout flare days per patient were significantly higher in without prophylaxis group than other groups. Compared to colchicine group, gout flare days per patient in etoricoxib was lower (2.6±0.6 vs 1.2±0.5) (P<0.05) (**Table 2**).

Tolerability

Diarrhea was the most frequently reported side effect in patients receiving colchicine and more than 7 times as often compared with those receiving etoricoxib (10.7% vs 1.5%). Rates of

Table 2. Acute gout flare of patients in each group

Parameters	Without prophylaxis group	Etoricoxib group	Colchicine group
Gout flare days per patient			
Mean ± SD	8.2±2.8	1.2±0.5*,#	2.6±0.6*
Mean number of gout flares per patient			
Mean ± SD	8.1±1.3	3.2±1.8*,#	4.2±2.3*

*Compared to without prophylaxis group, $P<0.05$, #Compared to colchicine group, $P<0.05$.

Table 3. Summary of adverse events

Parameters	Etoricoxib group	Colchicine group
Diarrhea *n* (%)	2 (1.5%)	12 (10.7%)
Nausea and vomiting *n* (%)	4 (3.1%)	11 (9.8%)
Gastrointestinal and abdominal pains *n* (%)	7 (5.5%)	7 (6.2%)
WBC decrease *n* (%)	4 (3.1%)	3 (2.7%)
Abnormal liver function *n* (%)	5 (3.9%)	8 (7.1%)
Edema *n* (%)	5 (3.9%)	2 (1.8%)
Hypertension *n* (%)	3 (2.3%)	2 (1.8%)
Skin rash *n* (%)	1 (7.8%)	2 (1.8%)
Neurologic signs and symptoms *n* (%)	0	1 (0.9%)

nausea and vomiting were 3 times higher in colchicine group compared with etoricoxib group (9.8% vs 3.1%). Several patients in etoricoxib group (5.5%) and colchicine group (6.2%) complained gastrointestinal and abdominal pain. Patients receiving colchicine had higher rates of gastrointestinal AEs than did those who received etoricoxib.

Abnormal liver function occurred in 3.9% patients in etoricoxib group and 7.1% in colchicine group. WBC decrease occurred in 3.1% patients in etoricoxib group and 2.7% in colchicine group. Edema occurred in 3.9% patients of etoricoxib group. Hypertension and skin rash occurred in individual patients of two groups (**Table 3**).

Discussion

Initiation of ULT paradoxically causes an increased risk of gout flares. Because after taking the drugs, the level of SU will drop suddenly. Tiny tophi in intra-articular spaces may dissolve and release insoluble needle-like crystals, which can cause the initial occurrence of acute gout [8-10]. Therefore, in order to decrease gout attacks after ULT, prophylaxis drug should be taken during this period. Our results showed that the frequency of gout attacks in etoricoxib group and colchicine group were significantly lower than that in no prophylaxis group. It indicated that prophylaxis could effectively reduce acute gout flares when ULT. Our results also showed that the percentage of the treatment-to-target ratio in without prophylaxis group was lower than other groups. The reason may be frequent acute flare make the patients have to reduce or interrupt ULT. It means that an increased rate of acute flares that could contribute to poor treatment adherence. So prophylaxis for flares induced by ULT is an important consideration in gout management.

Concomitant treatment with colchicine or NASID to prevent gout flares is recommended during the first several months of urate-lowering therapy. These two drugsare also commonly used to treat acute gout. Colchicine is an inhibitor of microtubule synthesis necessary for cell migration. Colchicine should be dosed modestly at 0.5-0.6 mg 1-2 times/day. Maduri S had reported ointments containing colchicine in low concentrations was a feasible and effective treatment option for the prevention and treatment of acute gout attacks [11]. Etoricoxib, a selective inhibitor of COX-2, has analgesic, anti-inflammatory and antipyretic effect, and can reduce gastrointestinal side effects and does not affect the function of platelet. Not only etoricoxib has the same efficacy on acute gout as indometacin and diclofenac but also it has a lower incidence of adverse events [12].

We compared the efficacy and safety of two drugs associated with treatment available to prevent an acute attack of gout during ULT. Compared to colchicine group, the mean number of acute gout flares per patient and gout flare days per patient in etoricoxib group was significantly reduced. These results suggest that etoricoxib was more efficacy associated with treatment available to prevent an acute

attack of gout when ULT. In terms of AEs, etoricoxib exhibited a lower incidence. The incidence of GI AEs was higher after colchicine treatment than with etoricoxib. Some patients of colchicine group suffered diarrhea, nausea and vomiting. Several patients in etoricoxib group complainted gastrointestinal and abdominal pain. Etoricoxib is tolerated better by patients than colchicine. These results suggest that etoricoxib was more safety associated with treatment available to prevent an acute attack of gout when ULT.

ACR guidelines recommend that most of the cases be prevented for 6 months; or if the patient has no gout stones, the level of uric acid is maintained for 3 months. Wortmann RL et al. reported gout flare data from the 3 Phase III trials of febuxostat found that flare prophylaxis for up to 6 months during the initiation of ULT appeared to provide greater benefit than flare prophylaxis for 8 weeks [13]. However, the long-term use of colchicine and NASID not only cause economic loss but also increase adverse reactions especially in the elder patients and patients whose liver function is abnormal. There is the study which suggests prophylaxis with low dose colchicine should be taken until the SU level reach or below the target value (package including a gout stone) [14]. Our results showed there was no significant difference in the proportion of patients who reported flares between the two prophylaxis groups and without prophylaxis group after reaching the target. This result may suggest prophylaxis may not be needed for a long time.

This study has several limitations. One is A variety of factors may contribute to acute gout flare. Potential patient factors include medical co-morbidities, concomitant medications, attitudes to disease and therapy, and poor adherence to urate-lowering therapy. Another factor that should be considered is Visual Analogue Scale (VAS) was not evaluated because of retrospective research. Last, there are the general limitations of observational and retrospective analyses. Although every effort was made to control for confounding differences in three groups, unobserved confounding factors may have led to bias that was not fully adjustable. In summary, our study found that the frequency of gout attacks in etoricoxib group and colchicine group were significantly lower than that in without prophylaxis group. Etoricoxib was more effective and safe in preventing acute attack when ULT. There was no significant difference between the two prophylaxis groups and without prophylaxis group after reaching the target. Additional experimental research is necessary to confirm these findings and/or determine an optimum initiation time for ULT. Further research into this area would also be useful to guide clinical practice.

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Disclosure of conflict of interest

None.

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