

Original article

Initiation of febuxostat for acute gout flare does not prolong the current episode: a randomized clinical trial

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Abstract

Objective. Our objective was to determine whether initiation of febuxostat during an acute gout flare prolongs the current episode.

Methods. In this randomized, placebo-controlled, single-blinded, multicentre trial, patients with acute gout flares within 72 h were randomized (1:1) to the placebo and febuxostat (40 mg/day) groups. All patients were administered diclofenac (150 mg/day) for 7 days and then open-labelled on the eighth day. Febuxostat 40 mg daily and diclofenac 75 mg daily were administered from day 8 through 28 for the remission period. The dose of diclofenac was 150 mg/day before remission in both arms, and the original protocol was maintained until remission. The primary outcome was 'days to resolution'.

Results. We randomized 140 patients, 70 into each arm. The mean days to resolution was 5.98 days [median 7.00, interquartile range (IQR) 2.45 days] for the placebo and 6.50 days (median 7.00, IQR 3.67 days) for the febuxostat group ($P = 0.578$). The rate of resolution within 7 days was 84.38% for the placebo group and 76.92% for the febuxostat group ($P = 0.284$). There were no statistically significant differences in joint pain, swelling, tenderness and erythema scores at days 1, 3, 5 and 7. The mean serum uric acid levels were 507.54 and 362.62 $\mu\text{mol/l}$ for the placebo and febuxostat group, respectively, on day 7 ($P = 0.000$). The rate of recurrent gout flares was 10.00% for the placebo group and 6.56% for the febuxostat group from day 8 through 28 ($P = 0.492$).

Conclusion. Initiation of febuxostat administration during an acute gout flare did not prolong the duration of acute flares.

Trial registration. Chinese Clinical Trial Registry, <http://www.chictr.org.cn/>, ChiCTR1800015962

Key words: febuxostat, gout, randomized clinical trial

Rheumatology key messages

- The initiation of febuxostat during an acute gout flare did not prolong the current episode.
- The rate of 'treat to target' was higher in the febuxostat group on day 7.
- The rate of recurrent gout flares did not increase in the febuxostat group.

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Introduction

Gout is a common arthritic condition that results from monosodium urate (MSU) crystal deposition. Urate-lowering treatment (ULT) is important for patients with gout. Previous guidelines have provided conflicting recommendations on whether ULT could be initiated during an acute gout flare [1–3]. Generally, ULT should be initiated after an acute flare has resolved to avoid prolongation of symptoms [4]. The incidence of gout flares has been positively correlated with the reduction of serum uric acid (sUA) levels in the first few months after initiating ULT [5].

However, ULT could be initiated during an acute flare to reduce the number of outpatient treatment visits

required, and hence increase patient compliance [6–8]. The 2016 EULAR Gout Management Recommendations have not provided clear guidance on this [9]. In addition, the 2020 American College of Rheumatology (ACR) Guidelines for the management of gout have conditionally recommended that pharmacological urate-lowering therapy could be initiated during an acute gout flare based on anti-inflammatory treatment [3]. However, this recommendation was graded moderate based on two small randomized clinical trials [10, 11] and an observational study [12].

Two small randomized clinical trials observed that initiating allopurinol treatment during an acute gout flare did not prolong painful gout flares [10, 11]. Febuxostat (40 mg/day) had a superior urate-lowering effect compared with limited allopurinol doses (maximum 200–300 mg/day) [5, 13]. At present, no studies have been published regarding the initiation of febuxostat for acute gout flares. Our objective of this study was to determine whether the initiation of febuxostat during an acute gout flare prolongs the current episode.

Methods

Study design and participants

This was a randomized, placebo-controlled, single-blinded, multicentre study conducted from June 2018 to November 2019 (trial registration: chictr.org.cn, ChiCTR1800015962). This study was approved by the Institutional Medical Ethics Committee of the Fourth Clinical Medical College of Guangzhou University of Chinese Medicine. Informed written consent was obtained from all study participants. Patients were blinded and enrolled from three Chinese hospitals. Male and female patients, 18–70 years of age, with an onset of acute gout flares within 72 h were enrolled. These patients met the American College of Rheumatology criteria for acute arthritis of gout [14]. Patient exclusion criteria were as follows: secondary gout (chronic kidney disease, blood disorders, etc.), a history of congestive heart failure, anticoagulant use, presence of gastrointestinal ulcers, patients with estimated glomerular filtration rates (eGFR) of <50 mL/min, aspartate and alanine aminotransferases (AST/ALT) or alkaline phosphatase levels >1.25 times the upper limit of normal, or patients who were administered steroids, colchicine, allopurinol, uricosuric drugs, chemotherapy, or immunosuppressive therapy in the past 3 months.

Intervention, randomization and blinding

One hundred and forty patients who met the study criteria were randomized at a 1:1 ratio without stratification. Patients were administered febuxostat 40 mg daily (febuxostat group) or placebo (placebo group). All patients were administered diclofenac (150 mg/day) for 7 days and then open-labelled on day 8. Febuxostat 40 mg daily and diclofenac 75 mg daily were administered from day 8 through 28 for patients in remission.

The dose of diclofenac was 150 mg/day before remission in both arms, the original protocol was maintained until remission.

A pre-allocated blocked randomization schedule was implemented using a block size of four. Eligible participants were randomized in a 1:1 ratio to either the febuxostat or the placebo group. Patients were enrolled by study site personnel. Each centre (hospital) recruited study participants by means of competition. The College of Public Health Management of Southern Medical University was designated as the ‘random centre’ to manage and perform the randomization process. To ensure representativeness, each centre enrolled at least 28 subjects. Each centre had a principle investigator (PI) who knows the treatment code, and another doctor who did not know the treatment code was responsible for assessing inflammation and recording the data. Before any of the study subjects were assigned to a group, the PI requested a randomized number from the ‘random centre’. Medications were self-administered at home and participants were blinded to the treatments assigned.

Outcomes

Primary outcome

The primary outcome was the ‘days to resolution’ from enrolment to the resolution of an acute gout flare. The resolution of an acute gout flare was determined if the patient had an absence of joint pain, swelling, tenderness and erythema. Flares were defined as one or more than one manifestation of joint pain, swelling, tenderness and erythema.

Secondary outcomes

Clinical observers assessed joint pain (5-point Likert scale: 0 = no pain, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe), joint swelling (4-point Likert scale: 0 = no swelling, 1 = probable swelling, 2 = visible, 3 = bulging beyond the joint margins), joint tenderness (3-point Likert scale: 0 = no tenderness, 1 = patient declares pain, 2 = patient declares pain and withdraws limbs) and joint erythema (3-point Likert scale: 0 = normal, 1 = suspect, 2 = redness) at baseline. Due to rapid changes in inflammation of gout and it was difficult for the subjects to come to the hospital every day for the first 7 days, we assessed joint inflammation on days 1, 3, 5 and 7, and we assessed joint inflammation on days 2, 4 and 6 by video calls in order to ensure the accuracy of the primary outcome (days to resolution). Other outcomes that were evaluated included sUA, ESR, CRP at baseline and day 7, and adverse effects on day 28.

Statistical analysis

The sample size was estimated using the nQuery Advisor software. Preliminary studies demonstrated that

the duration of gout flares were 17.00 days (s.d. = 8.53) in the Allopurinol group and 12.53 days (s.d. = 7.73) in the placebo group [10]. Thus, the mean difference was expected to be 4.47, and the s.d. of 8.53 was selected to ensure a sufficient sample size. The test level was a two-sided *P*-value of 0.05, power of 80%, and the ratio of the febuxostat, and the placebo group was 1:1. The estimated sample size for each group was 63 and was 126 in total for the two groups. In this study, the shedding rate did not exceed 10%, and the sample size for each group was determined to be 70. To ensure representativeness, at least 28 patients were enrolled from each centre.

Multiple imputation was used to manage missing values. The maximum missing rate of all variables is about 0.08, and the missing rates of the primary and secondary indicators (days to resolution, joint pain, joint swelling, joint tenderness and joint erythema) in this study were <0.04. Study populations included the intent-to-treat (ITT) analysis set, defined as all randomized patients; the per-protocol (PP) analysis set, defined as all patients in the ITT population without any major protocol deviations. The centre effect of the primary outcome was analysed using meta-analysis and logistic regression. The primary outcome and secondary outcomes were compared between the groups using Mann–Whitney U analysis. The proportion of recurrent gout flares, resolution within 7 days, and digestive disability between days 8 and 28 were compared between the groups using Pearson's χ^2 tests. A two-tailed significance level of 0.05 was used for all tests. We compared baseline characteristics between the study arms using the *t* test for continuous variables and the χ^2 test for dichotomous variables. Data were analysed using SPSS (version 22; SPSS Inc., Chicago, IL, USA) and Graph Pad Prism version 8 (San Diego, CA, USA).

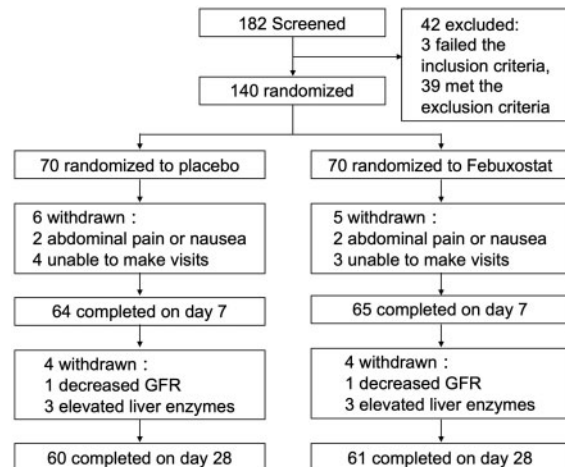
Results

Characteristics of the subjects

A total of 182 patients were screened, of which 42 patients were excluded. Three patients did not meet the inclusion criteria: acute gout flares for >72 h. Thirty-nine patients were excluded for the following reasons: 19 patients had taken anti-inflammatory drugs, six patients had taken ULT drugs in the last 6 months, eight patients had decreased GFR levels, two patients had secondary hyperuricemia and one patient, despite signing the informed consent form, did not agree to participate in the study. In total, 129 subjects completed the study until day 7 and 121 completed the study until day 28 (Fig. 1).

One hundred and forty patients were randomized, with 70 allocated to the febuxostat group and 70 allocated to the placebo group. The baseline characteristics of the study participants were similar between the two groups (Table 1). There were two female patients in each group. The mean age was 41.41 years of age in

Fig. 1 Flowchart of enrolment



In total, 182 patients were screened, with 42 patients excluded. Three patients did not meet the inclusion criteria: acute gout attack for >72 h. Thirty-nine patients were excluded for the following reasons: 19 patients had taken anti-inflammatory drugs, six patients had taken ULT drugs in the last 6 months, eight patients had decreased GFR, two patients had secondary hyperuricemia and one patient, despite signing the informed consent form, did not agree to participate in the study. A total of 129 completed on day 7, 121 completed on day 28.

the placebo group and 42.13 years of age in the febuxostat group ($P = 0.756$). The mean disease duration was 3.46 and 3.77 years in the placebo and febuxostat group respectively ($P = 0.692$). The rates of tophi involvement were 10.00% in the placebo group and 12.86% in the febuxostat group ($P = 0.595$). The mean duration of a gout flare prior to enrolment was 1.93 days for the placebo group and 2.07 days for the febuxostat group ($P = 0.255$). The most common affected joints were the ankles in the placebo group (42.86%), and the first metatarsophalangeal joint in the febuxostat group (47.14%).

Primary outcomes

There were no significant differences between the centres that affected the primary outcome determined using meta-analysis ($Z = 0.82$, $P = 0.41$) (Supplementary Fig. S1, available at *Rheumatology* online) and logistic regression ($P = 0.922$). The intent-to-treat analysis (Table 2) showed that the mean days to resolution was 5.98 days for the placebo group [range 1–19 days, median 7.00 days, interquartile range (IQR): 2.45 days] and 6.50 days for the febuxostat group (range 1–27 days, median 7.00 days, IQR: 3.67 days). There were no statistically significant differences ($P = 0.578$) between the two groups.

TABLE 1 Characteristics of study subjects

Parameters	Placebo (n = 70)	Febuxostat (n = 70)	P
Male, n (%)	68 (97.14)	68 (97.14)	1.000
Age (s.d.), years	41.41 (14.25)	42.13 (12.80)	0.756
Disease duration (S.D.), years	3.46 (4.46)	3.77 (4.97)	0.692
Tophi, n (%)	7 (10.00)	9 (12.86)	0.595
Attack time, (days)	1.93 (0.73)	2.07 (0.75)	0.255
Affected joint, n (%)			
Joints of the hand	2 (2.86)	5 (7.14)	
Wrist	2 (2.86)	3 (4.29)	
Elbow	4 (5.71)	3 (4.29)	
Knee	10 (14.29)	13 (18.57)	
Ankle	30 (42.86)	21 (30.00)	
Dorsal region of foot	3 (4.29)	5 (7.14)	
MTP1	29 (41.43)	33 (47.14)	

MTP: metatarsophalangeal.

The per-protocol analysis (Table 2) showed that the days to resolution was 6.16 days (range 1–19 days, median 7.00 days, IQR: 2.00 days) for the placebo group and 6.58 days (range 1–27 days, median 7.00 days, IQR: 4.00 days) for the febuxostat group ($P = 0.739$). The rate of resolution within 7 days was 84.38% for the placebo group and 76.92% for the febuxostat group [$P = 0.284$, odds ratio (OR) = 1.620, 95% CI: 0.667, 3.936].

Secondary outcomes

Manifestation scores

Pain scores for the placebo and febuxostat groups were 2.87 vs 2.89 ($P = 0.932$) at baseline. There were no statistically significant differences on days 1, 3 and 5. On day 7, the patient’s assessment of pain decreased to 0.13 vs 0.26 ($P = 0.057$) (Table 3). Initial mean joint swelling scores for the placebo and febuxostat groups were 1.99 vs 1.93 ($P = 0.700$). There were no statistically significant differences on days 1, 3 and 5. On day 7, joint swelling scores decreased to 0.13 vs 0.20 ($P = 0.468$) (Table 3). Initial mean joint tenderness scores for the placebo and febuxostat groups were 1.61 vs 1.60 ($P = 0.871$). There were no statistically significant differences on days 1, 3 and 5. On day 7, the joint tenderness scores decreased to 0.14 vs 0.19 ($P = 0.387$) (Table 3). Initial mean joint erythema scores for the placebo and febuxostat groups were 1.46 vs 1.40 ($P = 0.387$). There were no statistically significant differences on days 1, 3 and 5. On day 7, the joint erythema scores decreased to 0.10 vs 0.15 ($P = 0.550$) (Table 3).

Laboratory indicators

At baseline, the mean CRP levels were 17.16 mg/l for the placebo group, and 22.30 mg/l for the febuxostat group ($P = 0.225$). On day 7, CRP levels decreased to 7.59 versus 9.40 mg/L ($P = 0.513$) (Table 4).

TABLE 2 Days to resolution

Parameters	Placebo	Febuxostat	P
Intent-to-treat group ^a			
Mean (s.d.), days	5.98 (2.78)	6.50 (3.91)	0.578
Median (IQR), days	6.85 (2.45)	7.00 (3.67)	
Min, max, days	1, 19	1, 27	
Per protocol group			
Mean (s.d.), days	6.16 (2.78)	6.58 (4.02)	0.739
Median (IQR), days	7.00 (2.00)	7.00 (4.00)	
Min, max, days	1, 19	1, 27	
Resolution within 7 days, n (%)	54 (84.38)	50 (76.92)	0.284 ^Δ

^aITT dataset derived from multivariate imputation by chained equations with predictive mean matching; IQR: interquartile range; Δ : Pearson’s χ^2 tests.

TABLE 3 Manifestation scores for febuxostat vs placebo at baseline, days 1, 3, 5 and 7

Parameters	Placebo, mean (s.d.)	Febuxostat, mean (s.d.)	P ^a
Joint pain score			
Baseline	2.87 (0.99)	2.89 (0.99)	0.932
day 1	2.01 (1.20)	1.93 (1.22)	0.601
day 3	1.09 (1.01)	0.97 (1.04)	0.383
day 5	0.51 (0.65)	0.67 (0.81)	0.319
day 7	0.13 (0.42)	0.26 (0.50)	0.057
Joint swelling score			
Baseline	1.99 (0.88)	1.93 (0.87)	0.726
day 1	1.69 (0.93)	1.50 (0.96)	0.219
day 3	0.85 (0.79)	0.75 (0.76)	0.454
day 5	0.45 (0.63)	0.41 (0.55)	0.848
day 7	0.13 (0.34)	0.20 (0.47)	0.468
Joint tenderness score			
Baseline	1.61 (0.49)	1.60 (0.55)	0.970
day 1	1.36 (0.57)	1.22 (0.65)	0.207
day 3	0.73 (0.59)	0.58 (0.58)	0.149
day 5	0.38 (0.49)	0.45 (0.53)	0.458
day 7	0.14 (0.38)	0.19 (0.43)	0.387
Joint erythema score			
Baseline	1.46 (0.63)	1.40 (0.69)	0.704
day 1	1.14 (0.80)	1.00 (0.74)	0.288
day 3	0.46 (0.56)	0.38 (0.57)	0.283
day 5	0.26 (0.44)	0.30 (0.49)	0.659
day 7	0.10 (0.30)	0.15 (0.39)	0.550

^aCalculated from Mann–Whitney U test.

At baseline, the mean ESR was 19.82 mm/h for the placebo group and 16.97 mm/h for the febuxostat group ($P = 0.510$). On day 7, ESR was 17.61 mm/h for the placebo group and 17.41 mm/h for the febuxostat group ($P = 0.610$) (Table 4).

At baseline, the mean sUA levels were 538.94 $\mu\text{mol/l}$ for the placebo group and 517.34 $\mu\text{mol/l}$ for the febuxostat group ($P = 0.334$). On day 7, the mean sUA levels were 507.54 $\mu\text{mol/l}$ for the placebo group and 362.62

TABLE 4 The CRP, ESR and sUA in the baseline and day 7

Parameters	Placebo(n = 70)	Febuxostat(n = 70)	P
CRP, mean (s.d.), mg/l			
Baseline	17.16 (19.96)	22.3 (23.42)	0.225
day 7	7.59 (11.19)	9.40 (12.38)	0.513 [△]
ESR, mean (s.d.), mm/h			
Baseline	19.82 (16.19)	16.97 (14.49)	0.510
day 7	17.61 (16.84)	17.41 (20.42)	0.610 [△]
sUA, mean (s.d.), umol/l			
Baseline	538.94 (114.43)	517.34 (114.65)	0.334
day 7	507.54 (110.71)	362.62 (108.7)	0.000 [△]

sUA: serum uric acid; [△]: calculated from Mann–Whitney *U* test.

µmol/l for the febuxostat group. There were statistically significant differences between the two groups ($P = 0.000$) (Table 4). There were 36 (55.38%) patients whose sUA levels were lower compared with 360 µmol/l in the febuxostat group ($n = 65$). As expected, patients in the febuxostat group had lower sUA levels compared with the placebo group.

Adverse effects

Eight patients were withdrawn from the study due to adverse events on day 7. One patient had eGFR lower than 50 mL/min and three patients had elevated liver enzymes >2 times the upper limit of normal in each group. The remaining patients were followed up until day 28. The proportion of recurrent gout flares between days 8 and 28 were 10.00% (6/60) in the placebo group and 6.56% (4/61) in the febuxostat group ($P = 0.492$, OR = 1.583, 95% CI: 0.423, 5.920). The proportion of digestive disorders were 15.00% in the placebo group and 21.31% in the febuxostat group ($P = 0.368$, OR = 0.652, 95% CI: 0.255, 1.663). There were no serious adverse events.

Discussion

The response rate of patients with gout is about 80% within 7 days of using traditional non-selective non-steroidal anti-inflammatory drugs [15], with maximum 'days to resolution' being 28 days [10]. Hence, diclofenac was continued for 4 weeks in this study. We found that initiation of febuxostat administration during an acute gout flare did not prolong acute flares, and the rate of 'treat to target' was higher in the febuxostat group. This may increase patient compliance.

Two randomized clinical trials demonstrated that initiating allopurinol treatment during an acute gout flare did not prolong painful gout flares [10, 11]. In one of the trials, allopurinol was initiated at 100 mg daily for the first 14 days and then increased to 200 mg daily for the next 14 days [10]. The investigators observed that the days to resolution were 15.4 days for the allopurinol group and 13.4 days for the placebo group ($P = 0.05$). However, the sample cohort used in the study was small (17 in the

placebo and 14 in the allopurinol group), and the type of anti-inflammatory drugs used in the study increased the experimental uncertainty. In addition, the days to resolution coincided with the time it takes to spontaneously resolve inflammation during typical gout flares. In another published study, patients presenting within the first 7 days of onset of an acute gout flare were evaluated. The mean daily visual analogue scale (VAS) pain scores did not differ significantly between the study groups at any point between days 1–10. However, allopurinol was initiated at 300 mg daily, which was not consistent with the recommended guidelines, and inflammation was reflected only using VAS, and not by joint swelling, tenderness and erythema.

Several limitations to the current study need to be mentioned. First, this was a single-blinded trial. Although we tried our best to make the placebo look similar to febuxostat, some experienced observers could still distinguish between the placebo and experimental drug. The observational bias was inevitable. Second, although the sensitivity and specificity of the 2015 ACR/Eular criteria for gout [16] were higher compared with the 1977 acute gout classification criteria [14], due to the limitations of the three central examination centres, such as the use of dual-energy CT and the ultrasound model, the consistency of diagnosis in each centre could not be guaranteed. The 1977 acute gout classification criteria are also recognized and a commonly used standard in clinical trials, and it is not limited by the examination conditions. Hence, we used the 1977 acute gout classification criteria. Diclofenac is a commonly used non-steroidal anti-inflammatory drug and has more side effects, such as liver damage, kidney damage, gastrointestinal bleeding, etc. For this reason, the exclusion criteria may imply that patients had milder gout. Due to the inflammation changes rapidly and it was difficult for the subjects to come to the hospital every day for the first 7 days, we assessed joint inflammation on days 1, 3, 5 and 7, and we assessed joint inflammation on days 2, 4 and 6 by video calls. However, this may affect the accuracy of the data.

Finally, we observed that the initiation of febuxostat during an acute gout flare did not prolong the duration of the flare. The mean sUA levels in the febuxostat

group were lower compared with the placebo group, and the rate of recurrent gout flares did not increase in patients that were administered febuxostat.

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Data availability statement

Data are available upon reasonable request. For inquiries about data sharing, please send requests to sailing1980@126.com.

Supplementary data

[Supplementary data](#) are available at *Rheumatology* online.

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