Joint Bone Spine 82 (2015) 428–431

Available online at ScienceDirect www.sciencedirect.com

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Original article

Significance of the initiation time of urate-lowering therapy in gout patients: A retrospective research

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ARTICLE INFO

Article history:
Accepted 21 February 2015
Available online 9 October 2015

Keywords:
Gout
Urate-lowering treatments
Serum urate

ABSTRACT

Objective: To evaluate the efficacy and safety of the initiation time of urate-lowering treatments (ULT) in gout patients.
Method: We retrospectively reviewed patients who were diagnosed with gout and were treated with ULT for at least 3 years. They were divided into two groups: group 1: 123 patients initiating ULT during an acute attack of gout; group 2: 457 patients prescribed ULT after an acute attack. Both demographic and clinical characteristics associated with gout were analyzed.
Results: Comparing patients in group 1 versus group 2: the former exhibited a shorter duration of gout (6.3 ± 2.1 vs. 8.9 ± 3.3 years). At the baseline, there was no significant difference in mean serum urate (SU; 7.8 ± 1.4 mg/dL vs. 7.9 ± 1.9 mg/dL, respectively). SU target levels (< 6.0 mg/dL) were achieved by 66.7 and 65.6% of the patients, respectively. The duration from initiation of ULT until the SU target was attained was lower in group 1 than in group 2. During the first 12 weeks, patients on ULT in group 1 had higher attack rates than those in group 2. The incidence of chronic kidney disease increased in percentage in group 1 was lower than in group 2.
Conclusions: Our survey revealed that in patients experiencing acute gout, initiation of ULT decreased the time required to reach the target SU and the incidence of CKD, but the attack rate was greater in the first 12 weeks.

1. Introduction

Gout is a common form of arthritis characterized by the deposition of monosodium urate (MSU) crystals in the joints and other tissues. The presence of MSU crystals in and around joints can initiate an inflammatory response that may lead to recurrent episodes of acute gouty arthritis, which are characterized by debilitating inflammation and pain [1]. Furthermore, gout patients are likely to suffer multiple comorbidities, such as hypertension, obesity, and renal impairment. The rate of gout has been on the rise and increases with age [2]. Gout is now estimated to affect 150 million people in China, which has led to its recognizance as a significant public health problem [3].

The central strategy for management of gout is long-term serum urate (SU) lowering, which leads to dissolution of MSU crystals, prevention of acute gout attack, and regression of tophi. A 'treat to serum urate target' approach has been recommended in a number of gout treatment guidelines. These guidelines contend that, to prevent further gout episodes and enhance mobilization of urate deposits, SU should be lowered to < 6.0 mg/dL in patients with chronic gout and < 5.0 mg/dL in patients with tophaceous gout [4,5].

Proper management of the underlying hyperuricemia of gout is very important. A number of medications are useful for preventing further episodes of gout, including xanthine oxidase inhibitors (including allopurinol and febuxostat) and uricosurics (including probenecid and sulfinpyrazone) [6]. Traditionally, these drugs are not usually used until one to two weeks after an acute attack has resolved, because the sudden lowering of serum urate after initiating urate-lowering therapy (ULT) often triggers acute gout. In 2007, the British Society for Rheumatology guidelines recommend that ULT should be initiated one to two weeks after an acute gout to ensure complete control of symptoms (level C evidence) [7]. In 2011, clinical guidelines recommended that the initiation of ULT be at least 2 weeks after the acute attack. However, in 2012 ACR recommendations were that initiation of ULT may be reasonable even in the middle of a gout attack if an appropriate anti-inflammatory regimen is initiated [8]. This is an approach that runs counter to previous recommendations. Taylor et al. had reported allopurinol initiation during an acute gout attack could not increase recurrent

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http://dx.doi.org/10.1016/j.jbspin.2015.02.021
1297-319X/

flares [9]. In other words, the question of when to begin ULT to prevent and reverse urate deposition remains debatable. There are no data on the efficacy and safety associated with the initiation time of ULT with respect to gout in China. We investigated these aspects using a retrospective cohort design.

2. Methods

2.1. Patients

We retrospectively examined data on 580 patients who were diagnosed with gout and treated with ULT for at least 3 years during the period January 1999 to January 2014 in the outpatient clinics and ward at the Department of Rheumatology, the First Affiliated Hospital of Liaoning Medical College. Approval was obtained from an independent ethics committee.

The inclusion criteria for this study were as follows: patients had to have previously met the American College of Rheumatology preliminary criteria for the classification of acute arthritis of primary gout. Additionally, it was also required that the patients were able to insist on using ULT and following up. Based on the initiation time of ULT, patients were divided into two groups: group 1: those initiating ULT during an acute attack of gout, comprising 123 patients; group 2: those prescribed ULT after an acute attack of gout, comprising 457 patients. Patients on both groups received flare prophylaxis with loxoprofen 60 mg orally three times daily for 8 weeks after initiation of ULT.

2.2. Measurements

For the purposes of descriptive analyses, the following data were recorded: age, sex, body mass index (BMI), duration of gout, frequency of acute gout attacks, and the time from initiation of ULT until target serum urate levels of < 6.0 mg/dL (allopurinol was used as the drug of choice) were achieved. Laboratory analysis, including SU levels, was conducted at every outpatient visit. History of comorbidities such as hypertension (HTN), type II diabetes mellitus (DM), cardiovascular disease (CVD), chronic kidney disease (CKD) and urolithiasis were investigated after UTL at the follow-up visits. CKD was defined as glomerular filtration rate (GFR) less than 60 mL/min per 1.73 m^2 calculated by modification of diet in renal disease formula. A gout attack 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 an attack reported by a patient or directly diagnosed by a physician [10].

2.3. 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, BMI, SU, and number of years with gout. *t*-tests and Chi^2 analysis was used to compare all other categorical baseline variables. A significance level of 0.05 was used.

3. Results

3.1. Demographic and clinical characteristics

Patients on group 1 were predominantly male (96.7%), and had a mean age of 44.5 ± 6.5 years and a BMI of 32.2 ± 6.1 kg/m^2. The mean duration of gout was 6.3 ± 2.1 years. Patients on group 2 were predominantly male (97.4%), and exhibited a mean age of 52.9 ± 7.2 years and a BMI of 30.5 ± 5.6. The mean duration of gout was 8.9 ± 3.3 years. Patients in the former group were significantly younger than those in the latter. In addition, the difference in the duration of gout was significant. Other demographic and clinical characteristics were generally similar between the two groups (Table 1).

Table 1
Characteristics of patients in each group.

Parameters	Group 1 (ULT during acute attack) *n* = 123	Group 2 (ULT after acute) *n* = 457	*P* value
Gender *n* (%)			
Male	119 (96.7%)	445 (97.4%)	0.095
Female	4 (3.3%)	12 (2.6%)	0.230
Age (years)			
Mean ± SD	44.5 ± 6.5	52.9 ± 7.2	0.003
BMI (kg/m^2)			
Mean ± SD	32.2 ± 6.1	30.5 ± 5.6	0.151
Duration of gout (years)			
Mean ± SD	6.3 ± 2.1	8.9 ± 3.3	0.032
Mean serum uric acid (mg/dL)			
Mean ± SD	7.8 ± 1.4	7.9 ± 1.9	0.098
Number of flares before starting ULT			
Mean ± SD	18 ± 1.2	26 ± 2.3	0.054
Allopurinol dose, mg/day			
Mean ± SD	235 ± 87.6	241 ± 98.2	0.123
SU target *n* (%)	82 (66.7%)	300 (65.6%)	0.581
Time from initiation of ULT until target (months)			
Mean ± SD	2.5 ± 0.6	3.8 ± 1.2	0.004
Follow-up tophi *n* (%)	11 (9.2%)	44 (9.6%)	0.756
Follow-up chronic kidney disease *n* (%)	4 (3.3%)	31 (6.8%)	0.023
Follow-up hypertension *n* (%)	18 (15.1%)	77 (16.7%)	0.526
Follow-up diabetes mellitus *n* (%)	17 (14.3%)	65 (14.2%)	0.673
Follow-up cardiovascular disease *n* (%)	9 (7.6%)	37 (8.1%)	0.092

ULT: urate-lowering treatments; BMI: body mass index; SD: standard deviations.

3.2. ULT

At baseline, there was no significant difference in mean SU between patients on group 1 and those on group 2 (7.8 ± 1.4 mg/dL vs. 7.9 ± 1.9 mg/dL, respectively). There was no significant difference in the dosage of allopurinol between the two groups (235 ± 87.6 mg/day vs. 241 ± 98.2 mg/day, respectively) (Table 1).

3.3. Treat-to-target

Serum urate levels < 6.0 mg/dL (the SU target level) were achieved by 66.7% and 65.6% of the patients in the groups on ULT during and after an acute attack of gout, respectively. Although no statistically significant differences were observed in the urate-lowering efficacy rates between the two groups, the time that elapsed from the initiation of ULT until the SU target of ULT was lower in the former group than in the latter (Table 1).

3.4. Flare rates

Attack rates were comparable among patients. Among patients initiating ULT during an acute gout attack, attack rates during the first 4 weeks and weeks 4–8, 8–12, and 12–16 were 51%, 38%, 31%, and 27%, respectively. The corresponding values in the other group were 35%, 31%, 29%, and 23%. Attack rates were decreased in both groups after UTL. During the first 12 weeks, patients in the former exhibited higher attack rates than those in the latter. However, such