International Journal of
Rheumatic Diseases

International Journal of Rheumatic Diseases 2017; **20:** 497–503

ORIGINAL ARTICLE

Current gout treatment and flare in South Korea: Prophylactic duration associated with fewer gout flares

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Abstract

Aim: To evaluate treatment patterns and clinical factors affecting gout flare in South Korea.

Methods: We retrospectively examined data from 401 patients seen at nine rheumatology multicenter clinics, under urate lowering therapy (ULT) more than 6 months after stopping prophylactic medication. Demographic data, clinical and laboratory features were collected at the initiation of ULT, upon stopping prophylaxis, and 6 months after.

Results: The mean age was 52.2 years and mean disease duration was 25.0 months. The male-to-female count was 387 : 14. The most common ULT starting agent was allopurinol 83.8%. Colchicine (62.3%) was the most commonly prescribed prophylactic agent. During ULT, 134 of the 401 patients (33.4%) experienced at least one gouty attack in the period from stopping prophylaxis to 6 months later. The duration of prophylaxis was different between those with serum uric acid levels below 6 mg/dL and those over 6 mg/dL ($P = 0.001$). Of the 179 patients (44.6%) who attained target serum uric acid (SUA) levels (6 mg/dL) at the end of prophylaxis, those taking < 6 months of prophylaxis suffered more frequent flares than those taking it ≥ 6 months (42.9% *vs.* 26.3%, $P = 0.041$). The time interval to the first attack after stopping prophylaxis was shorter in the < 6 months group than the ≥ 6 months group (13.5 weeks *vs.* 22.5 weeks, $P = 0.007$).

Conclusions: Prophylaxis more than 6 months from initiation of ULT, and achieving target SUA (< 6 mg/dL) at the time of stopping prophylaxis is associated with fewer gout flares during ULT.

Key words: flare, gout treatment, prophylactic duration, serum uric acid.

INTRODUCTION

Gouty arthritis is inflammatory arthritis resulting from monosodium urate crystal accumulation in joints.[1] Hypertension, diabetes mellitus, hyperlipidemia and kidney disease are often associated with gout and contribute to mortality of gouty arthritis patients,[2–4] and

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the prevalence of gout is increasing.[5,6] In the acute phase, anti-inflammatory treatment is sufficient to control disease activity, but urate lowering treatment (ULT) should be started if there are more than two gouty attacks in 1 year, tophi/radiologic changes, polyarticular involvement, urate-associated nephritis, or persistent diuretic use.[7,8] Management of hyperuricemia in gout is important, but compliance with ULT is low. Causes of stopping ULT include paradoxical flare, patient's concerns about multi-drug intake, and insufficient use of prophylactic agents.[9,10] Successful management often is challenged by an increased risk of acute gout flares during the first week to month after initiation of ULT as a result of rapid changes in serum uric acid (SUA) levels. Progression to chronic gout can be caused by poor compliance, ineffectiveness, inability to tolerate prescribed regimens or suboptimal physician adherence.[9–12] We evaluated the treatment patterns in South Korea and gout flare developing during ULT after stopping prophylaxis.

METHODS

We retrospectively examined data from 401 patients seen at nine rheumatology multicenter clinics between January 2013 and June 2013. Potential study subjects were those seen at the rheumatology clinic with gouty arthritis, taking urate lowering agents, with ULT more than 6 months after stopping prophylactic medications. Patients were excluded if they had adrenal insufficiency, other rheumatic diseases such as osteoarthritis, or had irregular follow-ups after starting ULT.

The diagnosis of gouty arthritis depends on finding monosodium urate crystals by polarization microscope or American College of Rheumatology (ACR) classification criteria.[1] Demographic and clinical data (age, sex, disease duration, tophi and comorbidity) were collected by chart review. Disease duration was defined from the onset of the first gout attack to the time of starting ULT. Clinical (kinds of prophylaxis, kinds and doses of urate-lowering agents, presence of gout flare) and laboratory (SUA levels, fasting glucose, lipid profile and calculated creatinine clearance [CCr]) information were collected at the initiation of ULT, at the time of stopping prophylaxis, and at 6 months after stopping prophylaxis. Gout flare is defined by: (i) physician diagnosis; or by (ii) any three out of four criteria of patient-reported features (gout flare, joint pain at rest, swollen joint, warm joint).[13,14] Flares during the period from stopping prophylaxis to 6 months later were counted. The study was approved by the Institutional Review Board at each hospital and informed consent was waived.

Statistical analysis used SPSS (SPSS Inc., Chicago, IL, USA). Student's *t*-test, Pearson's chi-square analysis, and analysis of variance (ANOVA) test were used. Null hypotheses of no difference were rejected if *P*-values were < 0.05.

RESULTS

Four hundred and one patients were enrolled. The mean age was 52.2 years, the mean disease duration was 25.0 months, and the mean body mass index was 26.9. The male-to-female ratio was 387 : 14. Comorbidities included hypertension (43.1%), diabetes mellitus (16.2%), hyperlipidemia (33.9%), cardiovascular diseases (8.5%) and kidney diseases (12.7%). Tophus was present in 7.2%. The initial gout treatments were colchicine (56.9%), non-steroidal anti-inflammatory drugs (NSAIDs) (55.4%) and steroids (26.7%). Monotherapy was 56.6%, dual therapy 32.1%, triple therapy 6.4%, and none 0.02% ($n = 1$) (Table 1).

Table 1 Demographic and baseline characteristics

Total ($n = 401$)	
Age (years, mean ± SD) at starting ULT	52.2 ± 13.8
Sex (male: female)	387 : 14
Body mass index (kg/m^2)	26.9 ± 19.2
Disease duration (months)	25.0 ± 57.6
Comorbidity (*n*,%)	
Hypertension	173 (43.1)
Diabetes mellitus	65 (16.2)
Hyperlipidemia	136 (33.9)
Cardiovascular diseases	34 (8.5)
Kidney disease	51 (12.7)
Presence of tophi (*n*,%)	29 (7.2)
At onset time of gout	
Medication	
Colchicine	228 (56.9)
NSAIDs	222 (55.4)
Steroids	107 (26.7)
Serum uric acid (mg/dL)	8.1 ± 1.9
CCr (mL/min/1.73 m^3)	79.6 ± 31.1
Glucose (mg/dL)	112.9 ± 37.3
Total cholesterol (mg/dL)	194.3 ± 72.6
Triglyceride (mg/dL)	220.2 ± 139.8
High-density lipoprotein (mg/dL)	40.1 ± 8.6

NSAIDs, non-steroidal anti-inflammatory drugs; CCr, calculated creatinine.

Allopurinol was most frequently used when starting ULT (83.8%), febuxostat in 1.0%, and uricosuric agents in 15.5%. One patient had combined therapy (allopurinol + uricosuric agents). The mean dose of allopurinol was 140.6 mg, changed to 206.7 mg; febuxostat was 80.0 mg, changed to 65.4 mg; and benzobromarone was 37.9 mg changed to 46.9 mg at the end of prophylaxis. Two hundred and ten (62.5%) allopurinol initiators started from no > 100 mg/day and 19 (5.7%) started from more than 300 mg/day.

The initial prophylactic agents were colchicine (62.3%), NSAIDs (39.9%), and steroids (16.7%). Monotherapy was 72.8%, dual therapy 20.9%, triple therapy 1.5% and none 4.0% (n = 16). The mean SUA when starting ULT was 8.4 mg/dL, CCr was 80.1 mL/min/1.73 m^3. At the point when prophylaxis ended, the proportion of allopurinol users decreased to 77.1%, while febuxostat increased to 5.5% and uricosuric agents to 26.7%. Thirty-seven patients (9.2%) had combined therapy. The mean SUA level was 6.1 mg/dL (Table 2). One hundred and thirty-four patients among the 401 study subjects (33.4%) experienced at least one gouty attack in the 6 months period after prophylaxis ended: 32.1% of allopurinol initiators (n = 108/336), 50.0% of febuxostat (n = 2/4) and 38.7% of benzbromarone (n = 24/62).

In our study, mean SUA level was 6.1 mg/dL when prophylaxis ended (6.3 mg/dL in the gout flare group *vs.* 5.9 mg/dL in the non-flare group, P = 0.028, data not shown). We evaluated clinical factors by SUA level at the end of prophylaxis (< 5 mg/dL, 5~6 mg/dL, ≥ 6 mg/dL). The proportion of allopurinol was lowest in the < 5 mg/dL group, and of febuxostat or benzobromarone was highest in the < 5 mg/dL group (P = 0.000). One hundred and seventy-nine patients (44.6%) reached target SUA (6 mg/dL). The prophylactic durations differed significantly by SUA levels at the end of prophylaxis (Table 3).

We asked how long should we continue prophylaxis? So we evaluated the clinical characteristics of gout flare by prophylactic duration in the patients who attained target SUA levels at the end of prophylaxis. By duration of prophylactic treatment (< 6 months, ≥ 6 months), gout flares happened more in those who had < 6 months of prophylaxis (42.9%) than those who had ≥ 6 months (26.3%, P = 0.041). The time interval to the first attack was shorter in the < 6 months prophylaxis group than in the ≥ 6 months group (13.5 weeks *vs.* 22.5 weeks, P = 0.007) (Table 4, Fig. 1).

DISCUSSION

In this study, we investigated the current gout treatment patterns and flares during ULT in South Korea. Rheu-

Table 2 Medications and laboratory findings by treatment

Medications and findings	At starting ULT	At the end of prophylaxis	At 6 months after stopping prophylaxis
	(n = 401, mean ± SD)		
Hypouricemic agents			
Allopurinol (n,%)	336 (83.8)	309 (77.1)	294 (73.3)
Febuxostat (n,%)	4 (1.0)	22 (5.5)	29 (7.2)
Benzbromarone (n,%)	62 (15.5)	107 (26.7)	113 (28.2)
Dose of allopurinol (mg)	140.6 ± 61.2	206.7 ± 84.5	200.7 ± 89.5
Febuxostat (mg)	80.0 ± 0.0	65.4 ± 19.6	62.0 ± 20.2
Benzbromarone (mg)	37.9 ± 16.5	46.9 ± 15.8	48.5 ± 16.1
Combined medication (n,%)			
Colchicine	250 (62.3)		
NSAIDs	160 (39.9)		
Steroids	67 (16.7)		
Dose of colchicine (mg)	0.9 ± 0.3		
NSAIDs (mg)	448.1 ± 448.0		
Steroids (mg)	5.9 ± 5.1		
Serum uric acid (mg/dL)	8.4 ± 2.1	6.1 ± 1.5	5.8 ± 1.3
CCr (mL/min/1.73 m^3)	80.1 ± 31.5	79.5 ± 30.5	81.1 ± 32.8

Dose of hypouricemic agent, means of hypouricemic agents. Dose of combined medication, means of combined medications. NSAIDs were composed of 14 different drugs. Dose of methylpredinosolone was converted to equivalent prednisolone dose. ULT, urate lowering treatment; NSAIDs, non-steroidal anti-inflammatory drugs; CCr, calculated creatinine.

Table 3 Clinical characteristics by serum uric acid levels at the end of prophylaxis

Serum uric acid level(n = 374)	< 5 mg/dL (n = 87)	5 ~ 6 mg/dL (n = 92)	≥ 6 mg/dL (n = 195)	P-value[a]
Age (years, mean ± SD)	53.8 ± 13.4	51.9 ± 13.4	51.4 ± 13.9	0.389
Sex (male: female)	85 : 2	91 : 1	187 : 8	0.340
Body mass index (kg/m^2)	25.6 ± 3.1	25.9 ± 3.3	27.9 ± 25.7	0.734
Disease duration (months)	14.2 ± 32.0	22.5 ± 56.6	31.9 ± 67.2	0.054
Duration of prophylaxis (months)	16.3 ± 18.4	19.0 ± 21.7	11.0 ± 16.1	0.001
Comorbidity (n,%)				
Hypertension	44 (50.6)	40 (43.5)	80 (41.0)	0.327
Diabetes mellitus	15 (17.2)	21 (22.8)	26 (13.3)	0.128
Hyperlipidemia	33 (37.9)	38 (41.3)	51 (26.2)	0.018
Cardiovascular diseases	11 (12.6)	8 (8.7)	15 (7.7)	0.405
Kidney disease	10 (11.5)	11 (12.0)	29 (14.9)	0.669
Presence of tophi (n,%)	9 (12.2)	5 (6.1)	14 (8.5)	0.404
At the end of prophylaxis				
Hypouricemic agents				
Allopurinol (n,%)	51 (58.6)	70 (76.1)	166 (85.1)	0.000
Febuxostat (n,%)	13 (14.9)	3 (3.3)	4 (2.1)	0.000
Benzbromarone (n,%)	40 (46.0)	28 (30.4)	33 (16.9)	0.000
Dose of allopurinol (mg)	186.5 ± 89.1	219.0 ± 92.3	207.1 ± 81.4	0.115
febuxostat (mg)	64.6 ± 20.2	66.6 ± 23.0	70.0 ± 20.0	0.899
benzobromarone (mg)	46.4 ± 14.7	46.2 ± 15.0	50.0 ± 17.9	0.568
Serum uric acid (mg/dL)	4.2 ± 0.6	5.4 ± 0.2	7.2 ± 1.2	0.000
CCr (mL/min/1.73 m^3)	83.2 ± 30.3	81.5 ± 29.3	77.3 ± 31.0	0.471
Patients with gout flare after stopping prophylaxis (n,%)	28 (32.2)	26 (28.3)	71 (36.4)	0.378
Mean frequency of flare (\person)	0.4 ± 0.6	0.4 ± 0.7	0.5 ± 0.8	0.389
Time interval to the first attack (weeks)	16.5 ± 11.2	22.8 ± 14.7	22.0 ± 15.7	0.183

Dose of hypouricemic agents, means of hypouricemic agents; CCr, calculated creatinine.
[a]By analysis of variance and chi-square test.

matologists in nine hospitals were involved. The steady rise of diagnosed gouty arthritis is generally linked to an aging population with multiple comorbidities, the use of certain medications, and changes in diet and lifestyle.[3–6] In the UK, several underlying diseases were independently associated with a first gout flare.[2] For a gout flare, the hazard ratio (HR) of ischemic heart disease was 1.12, hypertension 1.15, and renal failure 1.33. The other UK reports[15] with the same database and New Zealand/UK[16] in admitted patients with gout showed prevalences of hypertension (19–52%), diabetes mellitus (10–27%), hyperlipidemia (4–20%), cardiovascular disease (14–39%) and kidney disease (4–27%). In this study, we had less prevalence of cardiovascular disease, and more of hyperlipidemia compared with previous reports.[2,15,16] These differences might be related to different study designs and racial differences. Previous results were from national databases using UK (THIN data) or New Zealand (NZMoH data), while our data were from a relatively small-sized group and confined to the patients with ULT. We counted gout flare during the period from stopping prophylaxis to 6 months later, and found no significant differences of any comorbid conditions between flare and non-flare groups (data not shown). Gaffo *et al.* developed a definition of flare in patients with gout.[13] They reported that having three or more positive criteria of the four proposed criteria yielded a high sensitivity (91%) and high specificity (82%). We used their criteria to define gout flare by patient symptom report or by physician diagnosis.

A study cohort of 5942 gout patients found allopurinol to be the most common agent and 32.3% of allopurinol users were taking a daily dose of < 300 mg.[17] In our study, allopurinol was also the most commonly used agent. The reasons causing the decreased proportion of allopurinol users, while other hypouricemic agent users increased at the end of prophylaxis are unknown. However, there is a possibility that physician decisions to change/add ULT agents was because of

Table 4 Clinical characteristics by duration of prophylaxis

Attained target uric acid level at the end of prophylaxis (n = 179)	< 6 months (n = 42)	≥ 6 months (n = 137)	P-value[a]
Age (years, mean ± SD)	52.4 ± 14.0	53.0 ± 13.3	0.809
Sex (male: female)	41 : 1	135 : 2	0.684
Body mass index (kg/m^2)	25.6 ± 2.9	25.8 ± 3.4	0.727
Disease duration (months)	24.8 ± 67.4	16.5 ± 37.8	0.314
Duration of prophylaxis (months, mean ± SD)	2.5 ± 1.6	22.4 ± 20.9	0.000
Comorbidity (n,%)			
Hypertension	20 (47.6)	64 (46.7)	0.918
Diabetes mellitus	5 (11.9)	31 (22.6)	0.129
Hyperlipidemia	14 (33.3)	57 (41.6)	0.338
Cardiovascular diseases	1 (2.4)	18 (13.1)	0.048
Kidney disease	5 (11.9)	16 (11.7)	0.968
Presence of tophi (n,%)	4 (12.1)	10 (8.1)	0.476
At the end of prophylaxis			
Hypouricemic agents			
Allopurinol (n,%)	27 (64.3)	94 (68.6)	0.600
Febuxostat (n,%)	2 (4.8)	14 (10.2)	0.278
Benzbromarone (n,%)	16 (38.1)	52 (38.0)	0.987
Dose of allopurinol (mg)	229.6 ± 82.3	198.4 ± 93.8	0.120
febuxostat (mg)	60.0 ± 28.2	65.7 ± 19.8	0.719
benzobromarone (mg)	45.3 ± 10.0	46.6 ± 15.9	0.744
Serum uric acid (mg/dL)	4.8 ± 0.7	4.8 ± 0.7	0.876
CCr (mL/min/1.73 m^3)	77.9 ± 26.2	84.3 ± 31.0	0.341
Patients with gout flare after stopping prophylaxis (n,%)	18 (42.9)	36 (26.3)	0.041
Mean frequency of flare/person	0.6 ± 0.9	0.3 ± 0.6	0.035
Time interval to the first attack (weeks)	13.5 ± 9.4	22.5 ± 14.0	0.007

Dose of hypouricemic agents, means of hypouricemic agents; CCr, calculated creatinine.
[a]By Student's t-test and chi-square test.

ineffectiveness in obtaining target SUA or adverse events. The 2012 ACR guidelines recommend the starting dose of allopurinol of 100 mg/day and under, to be gradually titrated every 2–5 weeks, and doses can be raised above 300 mg/day.[18] Our data showed that 62.5% of allopurinol initiators started from no > 100 mg/day, and the mean dosage of allopurinol at the end of prophylaxis was below 300 mg/day. This is a treatment pattern not just of our patient population but elsewhere. One-third of allopurinol initiators started on a dose no > 100 mg/day and the dose of allopurinol was rarely titrated up in the USA.[19]

Attaining target SUA levels (< 6 mg/dL) is important to prevent later gout flare during ULT.[6] Shoji *et al.* reported that 91 patients among 276 (34%) had at least one gouty attack after ULT for 1 year, and 87% of the patients with mean SUA (< 6.0 mg/dL) had no flare.[20] Our results were similar with gout flare (33.4%), and 69.8% (125/179) of the patients attaining target SUA at the end of prophylaxis had no flare. As in other countries,[9–12] gout management is frequently suboptimal in South Korea. Although it is well-known that attaining target SUA is required for good clinical outcomes in gout, this study showed that the target SUA is frequently not achieved in clinical practice.

While prophylactic treatment is an important influence in the patient's compliance and therapy outcome, the proper duration of prophylaxis is an open question. There are some recommendations: at least 1 year after SUA is normalized,[21] 1–3 months after uric acid is stabilized,[22] or at least 6 months.[23] The European League Against Rheumatism recommended the first month after starting ULT in 2006,[7] the British Society of Rheumatology recommended 6 months in the case of colchicine and < 6 weeks of NSAIDs.[8] Recently the ACR recommended at least 6 months after starting ULT, or according to tophi presence, 3–6 months after reaching targeting uric acid levels.[24] There is no consensus as to which agents should be used, and the duration of their use. In our study, the mean duration of prophylaxis was

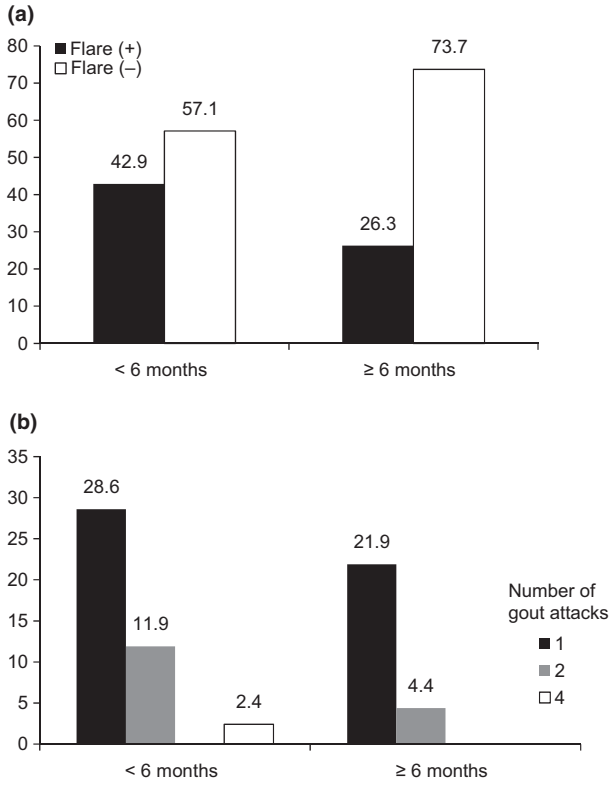

Figure 1 Cases (a) and frequency (b) of gout flare by duration of prophylaxis in patients achieving target uric acid levels at the end of prophylaxis (n = 179).

more than 1 year (14.0 months, data not shown) and colchicine was the most common initial prophylactic agent (62.3%). In a cohort analysis of 643 veterans, only 48% received colchicine or NSAID prophylaxis before or on the day of allopurinol prescription.[25] Although the authors in our study were all rheumatologists, there was no prophylaxis in 4.0% of patients. In the patients attaining target SUA at the end of prophylaxis, there were more frequent flares in the < 6 months prophylactic group than ≥ 6 months group, and the time interval to the first attack was also shorter in the < 6 months group. We conclude that more than 6 months prophylaxis is favorable to prevent gout flare in the period from stopping prophylaxis to 6 months later.

There are some limitations in our study because it was a retrospective study and the ethnicity is limited to Koreans, but we recruited patients from nine multicenter rheumatology clinics, and selected compliant patients who were regularly seen more than 6 months after stopping prophylaxis. Our patients represent typical patterns of gout treatment in South Korea and clinical factors affecting gout flare during ULT.

In conclusion, gout treatment in South Korea is suboptimal. Allopurinol and colchicine were the most commonly prescribed agents for gout treatment. Achieving target serum uric acid levels (< 6 mg/dL) when stopping prophylaxis and prophylaxis longer than 6 months is associated with fewer gout flares during ULT.

CONFLICTS OF INTEREST

None.

CONTRIBUTORS

HJC contributed to the design of the study, performed the analysis, interpreted the results and wrote the manuscript. HJB contributed to the design of the study, interpretation of the results and approval of final version of the manuscript. All authors contributed patients enrolled and data collected. The manuscript has been seen and approved by all the authors.

ETHICS APPROVAL

This study was approved by the institutional review board of each hospital involved.

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