Effect of Urate Lowering Therapy on Renal Disease Progression in Hyperuricemic Patients with Chronic Kidney Disease

Yoonjin Kim, Sungjoon Shin, Kyungsoo Kim, Sangtae Choi, and Kwanghoon Lee

ABSTRACT. ***Objective.*** To determine whether urate lowering therapy (ULT) could delay renal disease progression in hyperuricemic patients with chronic kidney disease (CKD).

Methods. We performed a retrospective review of hyperuricemic patients with stage 3 CKD followed from September 2005 to July 2014 in Dongguk University Ilsan Hospital, Goyang, Korea. A total of 158 eligible patients were identified and 65 of them were treated with ULT in addition to the usual CKD management. We divided the patients according to the use of ULT and compared the estimated glomerular filtration rate (eGFR) change from baseline value and the proportion of renal disease progression (decline of eGFR > 30% of the baseline value, initiation of dialysis or eGFR < 15 ml/min/1.73m^2) at the time of last followup. Risk factors for renal disease progression were identified by logistic regression analysis.

Results. After a median followup of 118.5 weeks (minimum 25, maximum 465), the ULT group showed better outcomes compared to the non-ULT group in terms of eGFR change from baseline (–1.19 ± 12.07 vs –7.37 ± 11.17 ml/min/1.73 m^2, p = 0.001) and the proportion of renal disease progression (12.3% vs 27.9%, p = 0.01). Goal-directed ULT showed better clinical outcomes compared to maintaining the initial ULT dose. Actual (area under the SUA-time curve adjusted by total observation time period) serum uric acid was significantly associated with the risk of renal disease progression (p for trend = 0.04) and actual serum uric acid level < 7 mg/dl reduced the risk of renal disease progression by 69.4%.

Conclusion. ULT significantly delayed renal disease progression in hyperuricemic patients with CKD. Goal-directed ULT seems to be better than continuing the initial ULT prescription. (First Release October 1 2015; J Rheumatol 2015;42:2143–8; doi:10.3899/jrheum.150067)

Key Indexing Terms:
HYPERURICEMIA CHRONIC KIDNEY DISEASES ANTIHYPERURICEMICS

Hyperuricemia associated with chronic kidney disease (CKD) has traditionally been considered an epiphenomenon of CKD. However, studies have revealed that hyperuricemia itself may have a pathogenic role in the progression of renal disease[1,2,3,4]. Hyperuricemia activates the renin-angiotensin system and inhibits the release of endothelial nitric oxide, thereby contributing to increased blood pressure and renal vasoconstriction[5,6]. In this regard, it is expected that urate lowering therapies (ULT) would be beneficial in preventing the progression of renal disease in CKD patients with hyperuricemia. Animal studies using models of nephrectomy and diabetic nephropathy have shown that correction of hyperuricemia with ULT decreased tubulointerstitial fibrosis[7,8,9]. A few human studies evaluated the use of ULT in CKD patients with hyperuricemia and suggested the value of ULT in slowing renal disease progression[10,11,12,13]. However, most of the relevant studies were relatively small in sample size and used different ULT treatment protocols, and some studies did not observe patients with CKD long enough to see the progression of renal disease. Currently, more data are needed to establish the value of ULT in CKD patients with hyperuricemia. In our current study, we aimed to determine whether ULT could delay the progression of renal function decline in hyperuricemic patients with CKD, and to evaluate the value of goal-directed ULT.

MATERIALS AND METHODS

Study population. We retrospectively reviewed the medical records of

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patients who were diagnosed as having CKD and concurrent hyperuricemia from September 2005 to July 2014 in Dongguk University Ilsan Hospital, which is a tertiary referral medical center located in the city of Goyang, an urbanized satellite town of Seoul, Korea, that has more than a million residents. Inclusion criteria for a relevant case were (1) stage 3 CKD: moderate reduction in glomerular filtration rate (GFR) defined as GFR values 30–59 ml/min/1.73 m^2; (2) hyperuricemia: serum uric acid (SUA) level > 7.0 mg/dl for males and > 5.7 mg/dl for females; (3) duration of followup longer than 6 months; and (4) duration of treatment with ULT longer than 6 months for patients who were treated with ULT. Patients with the following conditions were excluded from analysis: acute medical conditions that may affect kidney function, acute kidney injury, nonrenal conditions that were reported to be associated with hyperuricemia (psoriasis, hemolytic anemia, lymphoproliferative disease, rhabdomyolysis, diabetes insipidus, hyperthyroidism, and hypothyroidism), and polycystic kidney disease, a condition in which no specific treatment has been proven to prevent or delay renal disease progression. After searching for relevant cases from the electronic medical system and applying the inclusion and exclusion criteria, we finally found a total of 158 eligible patients, and 65 of them were treated with ULT during the followup period. Details of patient selection are presented in Figure 1.

Description of treatment with ULT. All patients with CKD were treated and followed by the nephrologists (K. Kim, S. Shin, Y. Kim) in Dongguk University Ilsan Hospital. Ninety-three patients received only the conventional treatment for CKD and the remaining 65 patients were treated with ULT in addition to conventional CKD treatment. Forty-two of the 65 patients treated with ULT had gout and were treated by a rheumatologist (K. Lee) in the same hospital. In these patients with gout, ULT was titrated or switched to other alternative drugs until the target uric level (< 6 mg/dl) was reached. The remaining 23 patients who had both hyperuricemia and CKD but not gout were managed by the nephrologists and the initial dose of ULT was maintained throughout the followup period.

Study outcomes. To assess the effect of ULT in slowing the progression of renal disease, we divided the patients into 2 groups: the ULT group (n = 65) and the non-ULT group (n = 93) and compared the changes of renal function from baseline to the timepoint of last followup as well as their annual changes. Estimated GFR (eGFR) calculated from serum creatinine using the Modification of Diet in Renal Disease Study equation[14] was used as a means of measuring renal function. In addition, we assessed and compared the proportion of patients with renal disease progression defined as the presence of at least 1 of the following: decline of eGFR > 30% of the baseline value, initiation of dialysis or eGFR < 15 ml/min/1.73 m^2. We investigated the levels of SUA at baseline and at the last followup. To determine the actual level of SUA during followup and to minimize the variability of SUA level, we calculated the area under the SUA-time curve and adjusted it by the total time period of observation. We named this value the "actual SUA." Finally,

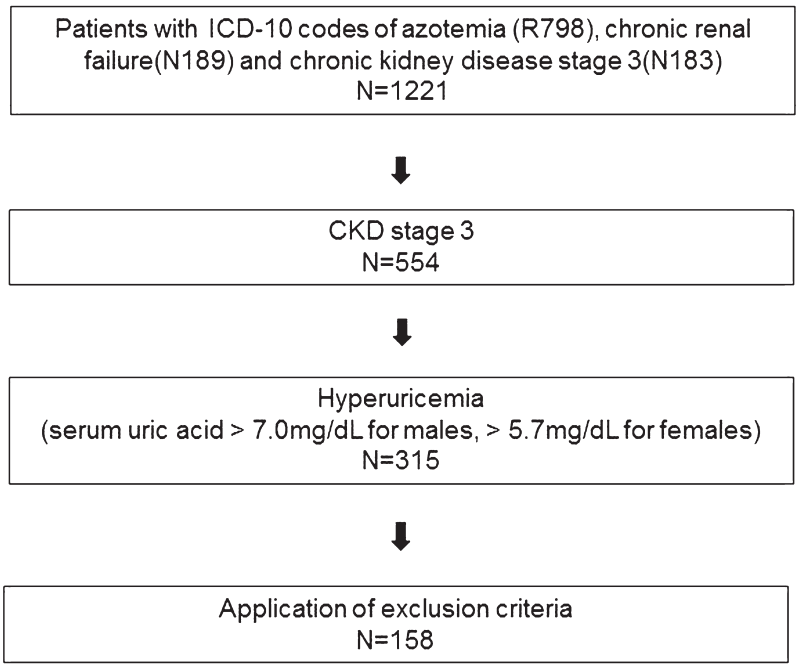

Figure 1. After searching the electronic medical record system for cases with ICD-10 codes for azotemia, chronic renal failure, and chronic kidney disease (CKD) stage 3, we investigated patients who had CKD stage 3 and concomitant hyperuricemia. We applied the exclusion criteria to the 315 patients with both conditions and finally identified a total of 158 relevant patients. ICD-10: International Classification of Diseases, 10th ed.

we intended to identify the risk factors of renal disease progression by logistic regression analysis. Confounding factors related to renal disease progression were investigated, such as hypertension (HTN), diabetes mellitus (DM), cardiovascular diseases, and use of concomitant medications including antihypertensive drugs and nonsteroidal antiinflammatory drugs.

Statistical analysis. With SPSS version 18.0, we used independent 2-sample t test and paired t tests to compare continuous variables with normal distribution. Wilcoxon's rank sum test was used to compare continuous variables with non-normal distribution. Chi-squared test was used to assess the association between categorical variables, and Fisher's exact test was applied in cases with expected count < 5. Repeated measures ANOVA was used to compare the annual changes of eGFR between the ULT and the non-ULT group. Binary logistic regression analysis was used to identify factors related to renal disease progression. Variables with p values < 0.09 in the univariate analysis were included in the binary logistic regression analysis. Missing data for variables that were measured in serial order were treated by last observation carried forward analysis and those for other variables were excluded from analysis.

Ethics statement. Our study was approved by the institutional review board of Dongguk University Ilsan Hospital, and informed consent was waived by the board because of the retrospective nature of our study.

RESULTS

Baseline characteristics. As shown in Table 1, both groups (non-ULT and ULT) were similar in age, proportion of male sex, duration of followup, baseline eGFR, and body mass index. Proportion of HTN and systolic blood pressure (SBP) were higher in the non-ULT group while the etiology of CKD and the use of antihypertensive drugs and low-dose aspirin were not different. SUA level was higher in the ULT group (9.05 ± 1.91 mg/dl vs 8.0 ± 1.16 mg/dl, p < 0.001) and patients with gout were included only in the ULT group (42/65, 65.63%).

Details of ULT treatment. In the 42 patients with both gout and CKD, most of the initially prescribed ULT was allopurinol, except in 1 patient who had previously experienced an allopurinol-induced severe cutaneous adverse reaction (SCAR). The initial starting dose of allopurinol ranged from 50 mg per day to 100 mg per day, with 100 mg per day being most common (38/41, 92.6%). The maintenance dose of allopurinol in patients with gout was 300 mg per day in 6 patients, 200 mg per day in 9, 150 mg per day in 3, and 100 mg per day in 13. Eight patients switched to febuxostat with a maintenance dose of 40 mg per day in 6 and 80 mg per day in 2. Two patients switched to benzbromarone with the maintenance dose of 50 mg per day. The reason for discontinuation of allopurinol was inefficacy in all cases. The maintenance dose of the patient who started with febuxostat was 40 mg per day. In the 23 non-gout patients with hyper-

Table 1. Baseline characteristics.

	Non-ULT treatment, n = 93	Treatment with ULT, n = 65	p
Age, yrs, mean ± SD	70.57 ± 12.41	66.92 ± 14.06	0.087*
Male sex, n (%)	66 (70.21)	54 (84.38)	0.064**
Duration of followup, days, mean ± SD	1066.35 ± 749.70	1027.56 ± 779.26	0.754*
Baseline eGFR, ml/min/1.73 m^2, mean ± SD	44.94 ± 8.09	44.70 ± 9.03	0.859*
Systolic BP, mmHg, mean ± SD	138.16 ± 24.96	129.54 ± 17.75	0.019*
Diastolic BP, mmHg, mean ± SD	79.51 ± 17.00	80.51 ± 13.79	0.699*
Associated disease, n (%)			
HTN	86 (91.49)	50 (78.13)	0.032**
CVD	20 (21.28)	20 (31.25)	0.219**
DM	40 (42.55)	20 (31.25)	0.204**
Dyslipidemia	57 (60.64)	43 (67.19)	0.503**
Baseline BMI, kg/m^2, mean ± SD	26.40 ± 15.91	27.78 ± 17.78	0.617*
Concomitant medications, n (%)			
ACEi	5 (5.32)	7 (10.94)	0.316**
ARB	44 (46.81)	22 (34.38)	0.164**
Low dose aspirin	45 (47.87)	27 (42.19)	0.588**
Diuretics	31 (32.98)	21 (32.81)	1**
NSAID	0 (0)	11 (16.92)	< 0.001**
SUA level, mg/dl, mean ± SD	8.00 ± 1.16	9.05 ± 1.91	< 0.001*
Etiology of CKD, n (%)			
Hypertensive	27 (28.72)	21 (32.81)	
Diabetic	39 (41.49)	17 (26.56)	
Glomerulonephritis	5 (5.32)	5 (7.81)	0.113**
Others	4 (4.26)	9 (14.06)	
Unknown	19 (20.21)	12 (18.75)	
Gout, n (%)	0 (0)	42 (65.63)	< 0.001

*** Independent 2-sample t test. **Chi-squared test. ULT: urate lowering therapy; eGFR: estimated glomerular filtration rate; BP: blood pressure; HTN: hypertension; CVD: cerebrovascular disease; DM: diabetes mellitus; BMI: body mass index; ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; NSAID: nonsteroidal antiinflammatory drug; CKD: chronic kidney disease; SUA: serum uric acid.

uricemia and CKD who were treated only by the nephrologists, most of the maintenance dose of allopurinol was 100 mg per day (21/23, 91.3%). None of these patients switched to febuxostat or benzbromarone. The baseline SUA level of these patients was significantly higher than that of the non-ULT group (9.7 ± 1.6 mg/dl vs 8.0 ± 1.1 mg/dl, p < 0.001) and the mean eGFR tended to be worse than that of the non-ULT group (41.2 ± 8.3 ml/min/1.73 m^2 vs 44.8 ± 8.1 ml/min/1.73 m^2, p = 0.056), which suggests that the nephrologists tended to prescribe ULT in patients with marked hyperuricemia out of concern that it may worsen renal dysfunction.

Clinical outcomes. After a median followup of 118.5 weeks (minimum 25, maximum 465), the ULT group showed better outcomes compared to the non-ULT group in eGFR change from baseline (–1.19 ± 12.07 vs –7.37 ± 11.17 ml/min/1.73 m^2, p = 0.001) and the proportion of renal disease progression (12.3% vs 27.9%, p = 0.01). When the eGFR values in each group were displayed annually, the eGFR values in the non-ULT group gradually worsened over time, while those of the ULT group did not. This trend was statistically significant based on the repeated measures ANOVA (p < 0.001). The SUA level declined from 9.05 ± 1.91 to 6.05 ± 1.71 mg/dl in the ULT group while that of the non-ULT group did not change (8.0 ± 1.16 to 8.0 ± 1.39 mg/dl). The actual SUA level was also significantly lower in the ULT group (7.02 ± 1.25 vs 7.90 ± 0.87 mg/dl, p < 0.001). The SBP remained significantly higher in the non-ULT group during followup. Allopurinol-induced SCAR was not noted during the followup period. The details of clinical outcomes are presented in Table 2. Nineteen patients achieved target SUA level (< 6 mg/dl) based on actual SUA level and showed substantially better outcomes than those who failed (Supplementary Table 1, available online at jrheum.org).

Subgroup analysis. We performed an additional analysis by subdividing the ULT group: (1) the goal-directed treatment group was composed of patients with gout in whom allopurinol was titrated or switched to other ULT to achieve serum acid < 6 mg/dl; and (2) the initial dose maintenance group was composed of non-gout patients in whom the initial dose of allopurinol was maintained throughout the followup period regardless of serum uric level. The outcomes of the goal-directed treatment group were still significantly better than those of the non-ULT group (eGFR change from baseline: –0.48 ± 13.03 vs –7.41 ± 11.22 ml/min/1.73 m^2, p = 0.002; proportion of renal disease progression: 11.9% vs 27.9%, p = 0.04), while those of the initial dose maintenance group were not (eGFR change from baseline: –2.54 ± 9.93 vs –7.41 ± 11.22 ml/min/1.73 m^2, p = 0.06; proportion of renal disease progression: 13% vs 27.9%, p = 0.18).

Logistic regression analysis of factors related to renal disease progression. We performed a univariate analysis of factors associated with renal disease progression (Supplementary Table 2, available online at jrheum.org) and found several significant factors: DM (p = 0.002), a history of cerebrovascular disease in the past (p = 0.03), admission during the followup period (p < 0.001), actual SUA (p = 0.04), and goal-directed ULT (p = 0.08). In the subsequent multivariate analysis (Table 3), DM was identified as an independent risk

Table 2. Clinical outcomes. Data are mean ± SD unless otherwise indicated.

	Non-ULT treatment, n = 93	Treatment with ULT, n = 65	p	
Baseline eGFR, ml/min/1.73 m^2	44.94 ± 8.09	44.70 ± 9.03	0.859*	< 0.001**
eGFR after 1 year, ml/min/1.73 m^2	41.51 ± 10.76	45.29 ± 11.26	0.038*	
p	< 0.001†	0.640†		
eGFR after 2 yrs, ml/min/1.73 m^2	39.42 ± 11.57	46.67 ± 11.94	< 0.001*	
p	< 0.001†	0.130†		
Last eGFR, ml/min/1.73 m^2	37.57 ± 12.01	43.51 ± 13.77	0.005*	
p	< 0.001†	0.417†		
eGFR change from baseline, ml/min/1.73 m^2	–7.37 ± 11.17	–1.19 ± 12.07	0.001*	
Renal disease progression, n (%)	26 (27.90)	8 (12.30)	0.019*	
Elapsed time from baseline to renal disease progression, weeks	147.76 ± 107.94	154 ± 125.40	0.892*	
SUA (baseline), mg/dl	8.00 ± 1.16	9.05 ± 1.91	< 0.001*	
SUA (last), mg/dl	8.00 ± 1.39	6.05 ± 1.71	< 0.001*	
Actual SUA, mg/dl	7.90 ± 0.87	7.02 ± 1.25	< 0.001*	
Systolic BP (baseline), mmHg	138.16 ± 24.96	129.54 ± 17.75	0.019*	
Systolic BP (last), mmHg	127.41 ± 15.98	121.19 ± 17.67	0.024*	
Diastolic BP (baseline), mmHg	79.51 ± 17.00	80.51 ± 13.79	0.699*	
Diastolic BP (last), mmHg	72.65 ± 11.08	72.17 ± 10.49	0.791*	
Controlled BP, n (%)	36 (38.7)	33 (51.5)	0.141††	

* Independent 2-sample t test. ** Repeated measures ANOVA. †Paired t test, comparison with baseline. †† Chi-squared test. ULT: urate lowering therapy; eGFR: estimated glomerular filtration rate; BP: blood pressure; SUA: serum uric acid.

Table 3. Multivariate analysis of factors associated with renal disease progression†.

Variables	Unadjusted OR (95% CI)*	p for trend	Adjusted OR (95% CI)**	p for trend
Goal-directed ULT				
No (reference)	1.000		1.000	
Yes	0.405 (0.146–1.129)		0.716 (0.225–2.274)	
DM				
No (reference)	1.000		1.000	
Yes	3.521 (1.6–7.748)		3.368 (1.399–8.109)	
CVA				
No (reference)	1.000		1.000	
Yes	3.161 (1.156–8.64)		2.062 (0.654–6.502)	
Admission during followup				
No (reference)	1.000		1.000	
Yes	4.251 (1.831–9.874)		2.428 (0.942–6.256)	
Actual serum uric acid		0.0169		0.0408
≥ 8.0 mg/dl (reference)	1.000		1.000	
< 8.0 mg/dl	0.502 (0.209–1.205)		0.471 (0.178–1.242)	
< 7.0 mg/dl	0.291 (0.099–0.855)		0.306 (0.089–1.059)	

† Renal disease progression is defined as the presence of at least 1 of the following: decline of eGFR > 30% of the baseline value, initiation of dialysis, or eGFR < 15 ml/min/1.73 m^2. * Estimated from the logistic regression model with each covariate (unit model). ** Estimated from the logistic regression model with all covariates (full model). ULT: urate lowering therapy; DM: diabetes mellitus; CVA: cerebrovascular accident.

factor of renal disease progression (OR 3.36, 95% CI 1.399–8.109) and there was a significant association between the actual uric acid level and the risk of renal disease progression (p for trend = 0.04). Actual SUA level < 7 mg/dl reduced the risk of renal disease progression by 69.4%.

DISCUSSION

In our study, ULT effectively lowered SUA levels and was associated with a significant delay in the progression of renal disease in patients with both CKD and hyperuricemia. Goal-directed ULT aiming at SUA level < 6 mg/dl seemed to be better than maintaining the initial ULT dose in slowing renal disease progression.

Renal disease associated with hyperuricemia or gout was traditionally believed to be due to the deposition of monosodium urate crystals (MSU) in the renal tissue. However, animal studies[5,6,15] found that hyperuricemia itself induces systemic and glomerular HTN as well as glomerular hypertrophy through a non-MSU–related mechanism and that allopurinol prevented the relevant renal changes associated with hyperuricemia. The role of ULT in renal disease progression gained much attention thereafter.

Goicoechea, *et al*[10] conducted a randomized trial of 100 mg allopurinol or usual therapy for 24 months in 113 patients with CKD and found that allopurinol-treated patients showed an increase in the mean eGFR (1.3 ± 1.3 ml/min/1.73 m^2) while control patients showed a decrease in the mean eGFR (3.3 ± 1.2 ml/min/1.73 m^2). Siu, *et al*[13] conducted a randomized trial of allopurinol 100 to 300 mg or usual therapy in 54 patients for 12 months. The proportion of renal disease progression was significantly less in the allopurinol group than in the control group (16% vs 46.1%, p = 0.01). Levy, *et al*[16], in their retrospective cohort study, demonstrated that hyperuricemia is an independent risk factor for renal function decline and patients who were treated with ULT and achieved SUA < 6 mg/dl showed a 37% reduction in the risk of renal disease progression. These results support the value of ULT in hyperuricemic patients with CKD.

Our study demonstrated that goal-directed ULT aiming at SUA < 6 mg/dl was better than maintaining the initial dose of ULT. Although goal-directed ULT showed only a weak association with renal disease progression (p = 0.08) in the univariate analysis, the risk of renal disease progression was significantly reduced as the actual SUA level decreased (p for trend = 0.04) in the multivariate analysis, which supports the value of goal-directed ULT in the management of hyperuricemia in patients with CKD. In addition, the change of eGFR from baseline was only –0.48 ± 13.03 ml/min/1.73 m^2 in goal-directed ULT group while that of the initial dose maintenance group was –2.54 ± 9.90 ml/min/1.73 m^2. However, it should be noted that the initial dose maintenance group was relatively small in size (n = 23) and clearly showed a trend (p = 0.06) to be clinically better than the non-ULT group in eGFR change from baseline. More data may be needed to clarify this issue.

A concern of allopurinol-induced SCAR may be raised about the use of ULT in patients with CKD. Oxypurinol, which is the main metabolite of allopurinol, has antigenic potential to induce SCAR and is excreted by the kidney[17]. This may explain why renal impairment is a risk factor of allopurinol-induced SCAR. In addition, Chung, *et al*[18] demonstrated in their cohort study that impaired renal function and increased plasma levels of oxypurinol and granulysin were significant risk factors for poor prognosis of

allopurinol-induced SCAR. In contrast, Fleeman, *et al*[19], in their systematic review about the use of allopurinol in patients with CKD, reported that the adverse events related to the use of allopurinol including SCAR are rare (2% of all users). The American College of Rheumatology[20] recommended that the dose of allopurinol could be raised above 300 mg per day even in patients with renal impairment provided that the patient is adequately educated about and monitored for adverse events. Of note, this may not justify the use of ULT in patients with CKD because the benefit of using ULT in asymptomatic hyperuricemia has not been fully established and does not outweigh the risk of allopurinol-induced SCAR. Therefore, the benefits of ULT on renal disease progression in hyperuricemic patients with CKD need to be firmly established in future studies.

Our study has several limitations. First, it is retrospective in nature and may have a risk of selection bias. Data on proteinuria, which is one of the major factors associated with renal disease progression, were unavailable in about half of all the cases and could not be analyzed owing to the large proportion of missing data. Second, the number of patients included was relatively small for comparing goal-directed ULT and the initial dose maintenance group. Third, the goal-directed ULT was applied only to patients with gout. Risks and benefits should be weighed when applying this strategy to CKD patients with asymptomatic hyperuricemia.

ULT significantly lowered the SUA levels and clearly showed a clinical benefit in slowing the progression of renal disease in CKD patients with hyperuricemia. Goal-directed ULT aiming at a SUA level < 6 mg/dl seems to be better than maintaining the initial dose of ULT. Further studies are needed to establish the value of ULT in CKD patients with asymptomatic hyperuricemia.

ONLINE SUPPLEMENT

Supplementary data for this article are available online at jrheum.org.

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