Outcome of Treatment in Gouty Arthritis Patients: A Retrospective Study

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Background: *Effective treatment in gouty arthritis can prevent joint and renal damage. Target serum uric acid levels of <6 mg/dl and <5 mg/dl are recommended in gouty arthritis and those with tophi, respectively.*

Objective: *To evaluate: (i) whether patients achieved recommended serum uric acid target and assess influencing factors and (ii) renal function between patients who achieved and not achieved the goal.*

Material and Method: *The medical records of gouty arthritis patients treated in outpatient department at Thammasat University Hospital between January 2013 and December 2013 were reviewed. Patients were divided into adequately (ATG) and inadequately treated groups (ITG) based on the ACR uric acid criteria after six months of treatment. Factors associated with inadequate treatment were explored and post treatment renal function compared between A and ITGs.*

Results: *Of 139 patients, 46 (33%) achieved target serum uric acid concentrations. Alcoholic consumption was the significant factor influencing the outcome. 75.5% of patients were followed-up >1 month for second evaluation of uric acid and most of them not receiving dosage up-titration even though not achieving the target. Both groups had similar alterations of renal function after treatment (p = 0.68).*

Conclusion: *Most patients failed to achieve recommended uric acid targets. Alcohol consumption was identified as a key risk factor for a suboptimal outcome. The treat-to-target approach should be underlined. Other risk factors should be explored prospectively.*

Keywords: *Gout, Outcome, Treatment, Serum uric acid level*

Gout is a common inflammatory arthritis with an increasing prevalence over the past decade[1-3]. It is caused by serum uric acid oversaturation and subsequent crystallization of monosodium urate. Hyperuricemia not only results in a destructive arthropathy that affects mainly small distal joints but also urate nephropathy and nephrolithiasis. Moreover, there is growing evidence that hyperuricemia may be associated with the development and progression of chronic kidney disease (CKD)[4-6]. Several trials demonstrate that lowering the serum uric acid in patients with gout improves and preserves renal function[7,8]. Therefore, the adequate treatment in lowering serum uric acid is essential to prevent these consequences. Accordingly, in 2012 the American College of Rheumatology (ACR) recommends treatment with urate lowering agents aiming for serum uric acid concentrations of <6 mg/dl and <5 mg/dl in gout and chronic tophaceous gout patients, respectively.

Data on result of gout treatment in Thailand are limited. Therefore, the present study was performed to assess the serum uric acid concentrations and renal function over a period of six month treatment in patients with gouty arthritis and identify the influencing factors.

Material and Method

This was a retrospective case note review of patients with a diagnosis of gout who were being followed-up at the outpatient department at Thammasat University Hospital (TUH) between January 1, 2013 and December 31, 2013. Patients were identified by a computerized ICD-10 search, looking for ICD code M10.0. Patients previously diagnosed at other hospitals were excluded in order to determine diagnostic methods pertaining to TUH. The study was approved by the institutional ethics committee. Data were collected onto

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a standardized case record form and included age, gender, body mass index (weight/height^2), previous medical illnesses, medications, alcoholic intake, diagnostic criteria for gout, presence of gouty tophi, uric acid concentrations over time, uric acid lowering agents, and glomerular filtration rate before and after six month treatment, times of the first follow-up appointment and number of patients who did not receive dosage up-titration, despite serum uric acid concentration not achieved.

The patients were divided into two groups based on whether they achieved the ACR recommended uric acid concentrations within six months of treatment i.e. serum uric acid <5 mg/dl and <6 mg/dl in patients with or without tophi, respectively [adequately treated group (ATG)], and serum uric acid ≥5 mg/dl and ≥6 mg/dl in patients with and without tophi [inadequately treated group (ITG)]. Variable factors were explored between the two groups.

The glomerular filtration rate (ml/min/1.73 m^2) was calculated by Cockroft-Gault formula and patients classified into five groups of chronic kidney disease: stages I GFR ≥90, II GFR 60-89, III 30-59, IV 15-29, V <15. The changes in renal function after treatment were compared between the two groups. Statistical analysis was done by using SPSS version 11.0. Student's t-test and Chi-square test were used to compare continuous and categorical variables between the two groups. The p-value <0.05 was considered statistically significance.

Results

One hundred and thirty-nine gouty arthritic patients were identified. Demographic and characteristics of all patients are shown in Table 1. There were 108 (77%) men and mean age was 61±13.06 (26-89) years. All were diagnosed by either clinical criteria and serum uric acid or joint fluid analysis and gouty tophi were present in 29 patients. The majority had at least one co-morbidity (63.3%) and a minority was alcohol consumers. Just under half of the patients had some degree of CKD with no difference between the two groups. Renal stones were identified in only 2 patients.

Almost all of the patients (96.5%) were prescribed allopurinol and the remainder were switched to benzbromarone due to allopurinol allergy. Drugs for co-morbidities were used, notably aspirin, diuretics, losartan, and fenofibrate in varying proportions. Of 139 patients, 105 (75.5%) were followed-up more than one month for the first time and most of them 118 (84.8%) had not received dosage up-titration even

Table 1. Characteristics of patients

Characteristics	n (%)
Body mass index (kg/m^2)	
<20	14 (10)
21-24.9	60 (43.1)
25-29.9	52 (37.4)
>30	13 (9.5)
Tophaceous gout	23 (16.5)
Diagnostic method	
Synovial fluid analysis	29 (21)
Clinical and serum uric acid	110 (79)
Medical illness	
Diabetes mellitus	23 (16.5)
Hypertension	88 (63.3)
Coronary artery disease	3 (2.1)
Cerebrovascular disease	14 (10.1)
Hypercholesterolemia (>200 mg/dl)	37 (26.6)
Hypertriglyceride (>150 mg/dl)	12 (8.6)
Chronic kidney disease (CKD)	
Stage I GFR >90 ml/min	79 (56.8)
Stage II GFR 60-89 ml/min	5 (3.5)
Stage III GFR 30-59 ml/min	32 (23)
Stage IV GFR 15-29 ml/min	20 (14.3)
Stage V GFR <15 ml/min	2 (1.43)
Renal stone	2 (1.43)
Alcoholic drinking	12 (8.6)
First follow-up >1 month	105 (75.5)
Non-dosage up-titration	118 (84.8)

though not achieving the serum uric acid target. Overall, 46 patients (33%) achieved the ACR target serum uric acid concentrations. In the analyses, only alcohol consumption was a significant factor between the A and ITGs (Table 2). An internal medicine physician was medically supervising more than half of the patients and there were no differences in types of follow-up physicians between the two groups (Table 3).

According to the stage of CKD, most of patients were in stage I (56.7%) stage III (23%), and stage IV (14.3%). Only 5.5% were in stage II (3.5%) and V (2%). The proportion of patients having increased GFR after treatment was not distinctive in either group (Table 4).

Discussion

The American College of Rheumatology guideline for the management of gout in 2012[9] recommended serum uric acid reductions of <5 and 6 mg/dl for patients with or without tophi, respectively. The present study showed that only one third (33%) of

Table 2. Comparison of variables between adequate and inadequate groups

Patient characteristic	Adequate group (n = 46)	Inadequate group (n = 93)	*p*-value
Age (years), mean (SD)	63.35 (13.3)	60.40 (12.8)	0.170
Male, n (%)	32 (69.5)	76 (81.7)	0.080
Female, n (%)	14 (30.4)	17 (18.2)	
BMI (kg/m²), mean (SD)	26.24 (5.1)	24.69 (3.9)	0.510
Initial uric acid (mg/dL), mean (SD)	10.14 (1.8)	8.74 (1.9)	0.140
Alcohol consumer, n (%)	0	12	0.015
Tophi appearance	4 (58.6)	19 (20.4)	0.076
Associated conditions, n (%)			
Hypertension	32 (69.5)	56 (60.2)	0.320
Diabetes mellitus	10 (21.7)	13 (13.9)	0.260
Coronary heart disease	0 (0)	3 (3.2)	0.220
Cerebrovascular disease	7 (15.2)	6 (6.4)	0.080
Dyslipidemia	15 (32.6)	33 (35.4)	0.920
Uric lowering agents, n (%)			
Allopurinol	43 (93.4)	91 (97.8)	0.410
Benzbromarone	3 (6.5)	2 (2.1)	0.230
Other medications, n (%)			
Aspirin	18 (39.1)	23 (24.7)	0.083
Diuretics	4 (8.6)	8 (8.6)	0.392
Losartan	10 (21.7)	10 (10.7)	0.118
Fenofibrate	3 (6.5)	2 (2.1)	0.198

Table 3. Comparison between 2-treatment outcome groups categorized by physicians specialties

Specialties, n (%)	Adequate group (n = 46)	Inadequate group (n = 93)	*p*-value
Internal medicine	28 (60.8)	57 (61.2)	
Rheumatologist	12 (26.1)	17 (18.3)	
General practice	4 (8.6)	11 (11.8)	
Orthopaedist	2 (4.3)	8 (8.6)	0.58

Table 4. Comparison of CKD stages and eGFR after 6-month treatment between 2-treatment outcome groups

Kidney function	Adequate group (n = 46)	Inadequate group (n = 93)	*p*-value
CKD stage			
I	30 (65.2)	50 (53.8)	
II	1 (2.2)	4 (4.3)	
III	6 (13.0)	26 (27.9)	
IV	9 (19.6)	11 (11.8)	
V	0	2 (2.1)	0.168
eGFR after treatment			
Increased	30 (65.2)	41 (44.1)	
Decreased	12 (26.1)	27 (29.0)	
Not change	4 (8.6)	25 (26.8)	0.688

the patients at a Thai teaching hospital achieved those after six months of treatment. There were several influencing factors: first, alcohol consumption was found to be the most important factor affecting inadequacy of treatment. Although, approximately 70% of patients were treated and followed-up by internal medicine and general practitioners, most patients were re-evaluated for serum uric acid level later than one month after initial treatment. According to 2006 EULAR evidence based recommendation for gout management[10], urate-lowering agent dosage should be increased every 2-4 weeks until serum uric acid concentration is achieved. Thus, the interval of second

evaluation was too long. Finally, the appropriate dosage up-titration should be strictly performed aiming for the target serum uric acid levels. These were indications that the importance of treat-to-target approach was not generally recognized by the physicians.

Several studies showed an association between serum uric acid concentration and progression

of chronic kidney disease in IgA nephropathy[11], diabetic nephropathy[5], and patients with normal renal function[12]. Hyperuricemia was also an independent risk factor for developing end stage renal disease in females[12]. Moreover, systematic reviews show that hyperuricemia is an independent predictor for the new-onset chronic kidney disease[13]. Levy et al[14] recently conducted a large retrospective cohort study with a 36-month, follow-up period and revealed that hyperuricemia was an independent risk factor for deterioration of kidney function. In addition, after treatment with urate lowering agent, the patients whose serum uric acid was <6 mg/dl had a 37% reduction in outcome events ($\geq$30% GFR decline from baseline or progression to ESRD). Siu et al[8] demonstrated that allopurinol could delay the progression of kidney disease by several mechanisms. They proposed that reducing serum uric acid might improve endothelial function, inactivate circulating platelets, increase nitric oxide production, and decrease glomerular hydrostatic pressure. Owing to short term follow-up and more than half of patients (57.5%) having CKD stage I, improvement of renal function was not demonstrated in ATG patients in the present study.

Regarding the accuracy of diagnosis, a previous study showed that 42% of patients, prescribed for allopurinol, were diagnosed in reference to American Rheumatism Association criteria[15]. The present study similarly underlined the diagnostic problem of gouty arthritis, only 30% of patients were diagnosed through synovial fluid analysis.

The present study has some limitations due to its retrospective design. Other potential factors influencing treatment outcome could not be assessed e.g. patients' medication compliance, diet control, and lifestyle modifications. These factors are important for the successful treatment of gouty arthritic patients.

Conclusion

This retrospective study has highlighted areas where the management of gout could be improved at TUH, in particular alcoholic consumption advice and better follow-up. A prospective study should be conducted to identify further factors for poor treatment outcomes and assess renal function improvement.

Potential conflicts of interest

None.

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การศึกษาย้อนหลังผลการรักษาผู้ป่วยโรคข้ออักเสบเกาต์

พันธุ์จง หาญวิวัฒนกุล, รัชพฤกษ์ วงษ์เดช

ภูมิหลัง: การรักษาผู้ป่วยโรคข้ออักเสบเกาต์อย่างมีประสิทธิภาพนั้นสามารถป้องกันการทำลายข้อและเนื้อไตได้ ทั้งนี้หลังการรักษาระดับกรดยูริกควรลดต่ำลงกว่า 6 มิลลิกรัม/เดซิลิตร หรือ 5 มิลลิกรัม/เดซิลิตร ในผู้ป่วยที่ไม่มีและมีก้อนโทฟัส

วัตถุประสงค์: เพื่อประเมินว่า 1) มีผู้ป่วยที่รักษาได้ตามเป้าหมายเป็นสัดส่วนเท่าไรหลังการรักษา และมีปัจจัยอะไรที่มีผลต่อผลการรักษา, 2) เปรียบเทียบการทำงานของไตระหว่างกลุ่มผู้ป่วยที่ผลการรักษาได้ตามเป้าหมายและกลุ่มที่ไม่ได้ตามเป้าหมาย

วัสดุและวิธีการ: ทำการทบทวนแฟ้มผู้ป่วยนอกของผู้ป่วยโรคข้ออักเสบเกาต์ที่มารับการรักษาที่แผนกผู้ป่วยนอก โรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติ ระหว่างเดือนมกราคม ถึง ธันวาคม พ.ศ. 2556 แบ่งผู้ป่วยออกเป็นสองกลุ่มตามผลการรักษาที่ 6 เดือนคือ กลุ่มที่ 1 ผู้ป่วยที่ระดับกรดยูริกได้ตามเป้าหมาย และกลุ่มที่ 2 ผู้ป่วยที่ระดับกรดยูริกไม่ได้ตามเป้าหมายจากนั้นวิเคราะห์หาปัจจัยที่มีความสำคัญต่อผลการรักษาและศึกษาเปรียบเทียบการทำงานของไตระหว่างผู้ป่วยทั้งสองกลุ่มด้วย

ผลการศึกษา: จากผู้ป่วย 139 รายมีเพียง 46 ราย (ร้อยละ 33) ได้ผลการรักษาตามเป้าหมายปัจจัยที่มีผลคือ การดื่มแอลกอฮอล์ ผู้ป่วยส่วนใหญ่ ร้อยละ 75.5 ได้รับการตรวจติดตามครั้งที่ 2 หลังการรักษาด้วยยาลดกรดยูริกซ์ คือ มากกว่า 1 เดือนขึ้นไปและพบว่าผู้ป่วยส่วนใหญ่ ไม่ได้รับการปรับเปลี่ยนขนาดยาแม้ว่าระดับกรดยูริกไม่ได้ตามเกณฑ์ ส่วนการเปลี่ยนแปลงของค่าการทำงานของไตหลังการรักษาในผู้ป่วยทั้งสองกลุ่มนั้นไม่แตกต่างกัน (p = 0.68)

สรุป: หลังการรักษาผู้ป่วยส่วนใหญ่ไม่ได้ระดับกรดยูริกตามเป้าหมาย การดื่มแอลกอฮอล์เป็นปัจจัยสำคัญที่ส่งผล และการรักษาผู้ป่วยควรมุ่งเน้นให้ได้ระดับกรดยูริกตามเกณฑ์ทั้งนี้ควรมีการศึกษาไปข้างหน้าเพื่อหาปัจจัยอื่น ๆ ที่มีอิทธิพลต่อผลการรักษาต่อไป