Are Target Urate and Remission Possible in Severe Gout? A Five-year Cohort Study

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ABSTRACT. ***Objective.*** Determine the proportion of patients achieving target serum urate (SU), defined as < 6 mg/dl for patients with non-severe gout and < 5 mg/dl for patients with severe gout, as well as the proportion of patients achieving remission after 5 years of followup.

Methods. Patients from the Gout Study Group (GRESGO) cohort were evaluated at 6-month intervals. Demographic and clinical data were obtained at baseline. Visits included assessments of serum urate, flares, tophus burden, health-related quality of life using the EQ-5D, activity limitations using the Health Assessment Questionnaire adapted for gout, and pain level and patient's global assessment using visual analog scales. Treatment for gout and associated diseases was prescribed according to guidelines and available drugs.

Results. Of 500 patients studied, 221 had severe gout (44%) and 279 had non-severe gout (56%) at baseline. No significant differences were observed across the study in percentages of severe gout versus non-severe gout patients achieving SU 6 mg/dl or 5 mg/dl. The highest proportion of patients achieving target SU (50–70%) and remission (39%) were found after 3–4 years of followup. In the fifth year, these proportions decreased and 28% of the patients were in remission, but only 40 patients remained in the study. None of the patients with severe gout achieved remission.

Conclusion. In patients with severe gout, target SU was hard to achieve and remission was not possible. The main obstacles for target SU and gout remission include poor medication adherence, persistent tophi, and loss to followup. (First Release August 15 2019; J Rheumatol 2020;47:132–9; doi:10.3899/jrheum.181214)

Key Indexing Terms:
TARGET URATE REMISSION GOUT SEVERE GOUT URIC ACID

Gout is the most common form of inflammatory arthritis, resulting from the deposition of monosodium urate crystals within joints or bursae. The estimated prevalence of gout in developed countries is ~3% in adults[1]. In Mexico, 90% of the population with gout are young men who frequently receive inadequate treatment for years before attending the rheumatology department[2,3]. Gout patients without adequate treatment have repetitive flares resulting in structural damage and disability[4]. Moreover, a high proportion of patients also have metabolic syndrome involving dyslipidemia, obesity, hyperglycemia/diabetes mellitus, and hypertension, with a subsequent increase in the frequency of renal disease and risk for cardiovascular and cerebrovascular conditions[5,6,7]. If left untreated or insufficiently treated, gout may become a disabling condition representing an overwhelming economic burden for patients and social security systems[8]. There is no widely accepted definition for severe gout, but in clinical practice this condition is characterized by frequent polyarticular flares, extensive tophaceous deposits, joint damage, and musculoskeletal disability[2]. The American College of Rheumatology (ACR) Management Guidelines defined severe chronic tophaceous gouty arthropathy as those cases with > 4 tophi, or at least 1 unstable, complicated, or severe tophus[9]. A threshold of 5 tophi has also been used in other studies to define gout as severe[10].

The key concept for effective management of patients

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with gout is that it is a reversible crystal deposition disease. Thus, the treatment is based on the reduction of serum urate (SU) levels and final elimination of monosodium urate (MSU) crystals[11]. Lower SU levels also increase the resolution rate of tophaceous deposits[12]. Several guidelines, including those published by the ACR and the European League Against Rheumatism (EULAR), recommend a target SU level < 6 mg/dl. In patients with more severe disease, a target SU level < 5 mg/dl is recommended to more rapidly improve gout signs and symptoms[9,13]. This prospective cohort study was aimed at determining the proportion of patients with severe gout and non-severe gout achieving target urate (TU) levels < 6 mg/dl and < 5 mg/dl, as well as the proportion of patients achieving remission after 5 years of followup.

MATERIALS AND METHODS

Study population. This is a prospective, longitudinal, observational cohort study of patients with gout starting in July 2010. All patients attending the Rheumatology Department of the Hospital General de México Eduardo Liceaga were invited to participate in this dynamic cohort of the Gout Study Group (GRESGO). The protocol and the informed consent were approved by the local Institutional Review Board/Ethics Committee (approval number DI/10/404/3/39). The study was conducted in accordance with the principles contained in the Declaration of Helsinki. All patients were informed about the procedures of the study and provided written informed consent during the baseline visit. During the period from 2010 to 2014, gout was diagnosed according to the Clinical Gout Diagnosis criteria[3]. Since 2015, the diagnosis of gout was based on the criteria of the ACR/EULAR[14]. In both instances, synovial fluid or tophi samples from patients were examined for the presence of MSU crystals.

Procedures. Demographic and clinical data including age at onset of gout, disease duration, and associated diseases were collected at baseline. Information about gout, lifestyle changes, and treatment was discussed with patients and relatives. Participants in the study were examined by the same physicians every 6 months or at shorter intervals if required. All visits included the investigation of SU (mg/dl); flares (no. episodes of acute arthritis in the last 6 mos); tophus burden (tophi number and index tophus size: the length in cm of the longest axis of the biggest accessible tophus); joint count: number of tender, swollen and limited-motion joints (44 count); Health Assessment Questionnaire (HAQ) score adapted for gout[4]; and health-related quality of life (HRQOL) using the EQ-5D[15]. The EQ-5D includes the following factors: (a) mobility, (b) self-care, (c) daily activities, (d) pain/discomfort, and (e) anxiety/depression. In addition, the EQ-5D included visual analog scale (VAS) for pain in a 10-cm scale (Pain-VAS) from 0 (no pain at all) to 10 (extreme pain), and patient's global assessment (PtGA), as indicated in a 10-cm VAS from 0 (being very well) to 10 (feeling very bad).

Treatment for gout and associated diseases was prescribed according to published guidelines[9] and available drugs. In the baseline visit, the patients received individualized prescriptions of urate-lowering therapy: 95% allopurinol and 1.4–7.5% probenecid because febuxostat was not available in Mexico until 2015. Patients were instructed to start oral allopurinol at 150 mg per day for 10 days, then escalate to 300 mg per day for 10 days, and remain with 450 mg per day until the following assessment. After SU level assessment, allopurinol was increased to 600 mg or even 750 mg per day in some cases. Patients had the option to telephone the study physicians, and if required, they could get immediate care at the clinic. The prophylactic dose of colchicine against gout flares of 1 mg per day was prescribed for longterm use if tolerated.

Variables and definitions. Severe gout was defined as the presence of ≥ 5 tophi and/or intradermal tophi at the baseline visit[10].

Target SU level was defined as < 6 mg/dl (0.36 mM) for patients with non-severe gout, and < 5 mg/dl (0.30 mM) for patients with severe gout.

The remission criteria for gout used here were those proposed by de Lautour, *et al*[16]. All criteria should be achieved at least twice over the last 12 months to meet the definition of remission: SU < 6 mg/dl (0.36 mM); tophus: none; flares: none; pain due to gout < 2 and no values > 2; and PtGA < 2 and no values > 2.

The assessment of patient's clinical outcome was according to the Outcome Measures in Rheumatology (OMERACT) domains for gout[17].

Gout flares were defined by the presence of at least 3 of the following criteria: patient-defined gout flare; pain score at rest > 3 on a 0–10 numeric rating scale; at least 1 swollen joint; and at least 1 warm joint[18].

Chronic kidney disease was considered in patients with glomerular filtration rate < 60 ml/min according to the Kidney Disease Improving Global Outcomes 2017 guidelines[19].

The Bronfman score was used for the assessment of socioeconomic status[20]. This tool evaluates housing characteristics (number of people and number of rooms in a dwelling, the type of construction, presence or absence of running water and sewers) and educational level of the head of household. The score ranges from 0 to 12, with 12 representing rudimentary housing conditions.

Statistical analysis. Quantitative variables were described with median and interquartile range (IQR), or with means ± SD; and categorical variables were described as proportions.

The Student t test was used for comparison of continuous variables of the group with severe gout versus the group with non-severe gout, and the chi-square test was used for comparison of categorical variables. The Friedman test was used for repeated-measures ANOVA. A 2-sided p value < 0.05 was considered significant. Only variables with a p value < 0.05 in univariate analyses were included in multivariate analyses. We also performed the Kaplan-Meier survival analyses of the time to SU < 6 mg/dl, the time to SU < 5 mg/dl, and the time to remission, comparing the group with severe gout versus the group with non-severe gout. All statistical analyses were performed using SPSS version 20 (SPSS Inc.).

RESULTS

Baseline characteristics of the study population. The GRESGO cohort includes a total of 500 patients with gout, of whom 97% were males. Of those, 221 had severe gout (44%) and 279 had non-severe gout (56%). MSU crystals were observed in the synovial fluid or tophi of 67% of the patients. There were significant differences between the severe gout and the non-severe gout groups on the baseline visit (Table 1). The severe gout group was significantly

Table 1. Baseline characteristics of the group with severe gout and the group with non-severe gout.

Variables	Severe Gout, n = 221 (44%)	Non-severe Gout, n = 279 (56%)	p
Age at onset, yrs, mean (SD)	31.3 (11.0)	36.4 (13.3)	< 0.001
Educational level, yrs, mean (SD)	8.7 (3.7)	9.5 (4.5)	0.039
Socioeconomic status, yrs, mean (SD)	8.3 (2.2)	8.7 (2.2)	0.018
Disease duration, yrs, mean (SD)	16.3 (10.3)	10.5 (10.1)	< 0.001
Disease duration prediagnosis, yrs, mean (SD)	7.9 (8.0)	6.4 (7.5)	0.023
Hypertension, %	47	37	0.001
Lithiasis, %	18	12	0.054
Chronic kidney disease, %	22	11	0.001
Use of self-prescribed glucocorticoids, %	43	20	< 0.01

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younger at onset, had lower educational and socioeconomic status, had longer disease duration, had more labor absenteeism, and had a higher frequency of hypertension and chronic renal failure. The severe gout group also had a significantly higher number of affected joints, a higher tophus burden, more activity limitations, and a lower HRQOL than did the non-severe gout group. In multivariate analysis, disease duration ($p = 0.008$) and flares ($p = 0.055$) remained significantly associated with severe gout.

The severe gout group received higher allopurinol doses than the non-severe gout group since the baseline visit, and this difference was significant during followup (Figure 1A). Individualized therapy with glucocorticoids (GC) was prescribed if required. In those patients using self-prescribed GC before the baseline visit, tapering regimens were implemented for withdrawal. The use of self-prescribed GC was more frequent in the severe gout group (43%) than in the non-severe gout group (20%) in the baseline visit ($p < 0.01$). Despite implementation of tapering regimens, the use of GC in the severe gout group was significantly higher than in the non-severe gout group during the first 6 months of followup (Figure 1B).

Changes in OMERACT domains for gout during followup. Since the first year, there was a significant improvement in both groups regarding the number of flares, tophus burden, functional class, pain level, HRQOL, and activity limitations

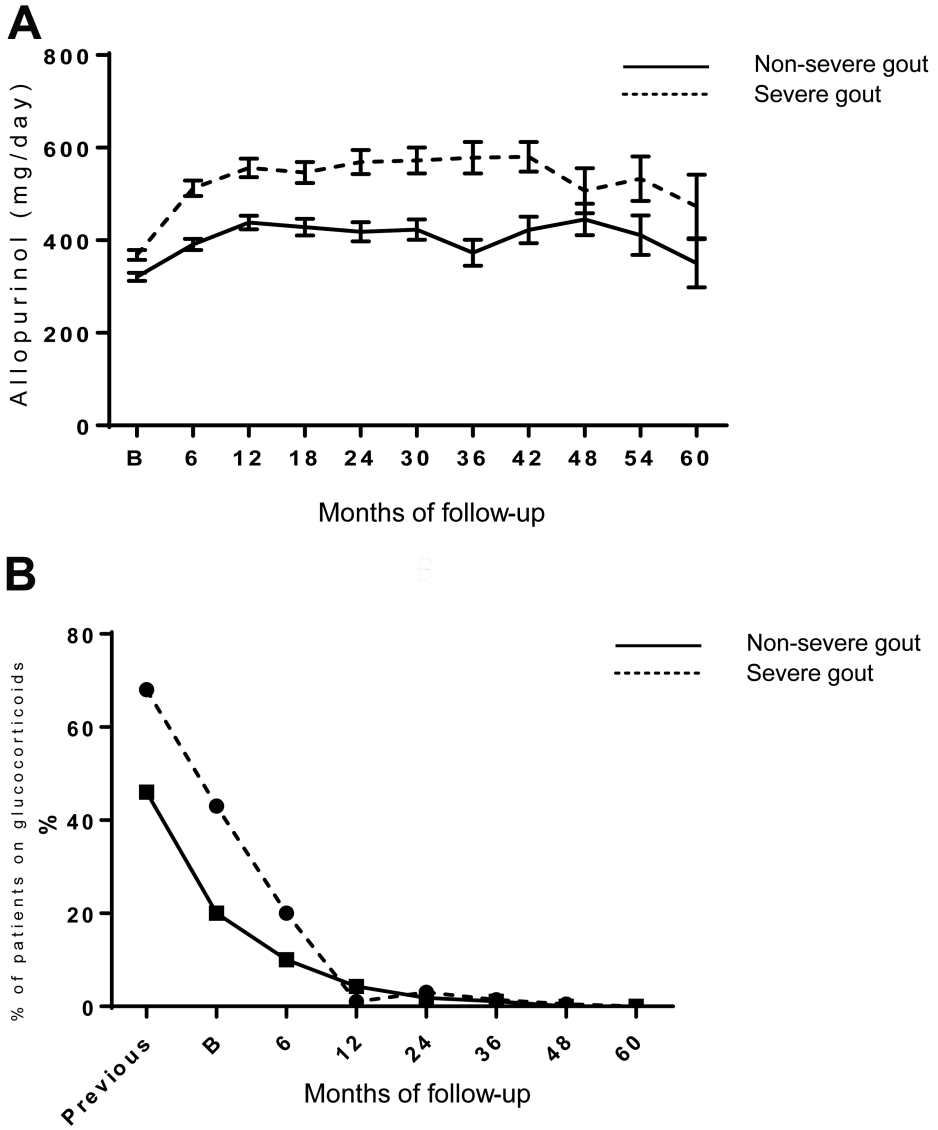

Figure 1. Use of allopurinol and glucocorticoids during followup. A. Allopurinol mean values ± standard error in the group with severe gout (dashed line) and the group with non-severe gout (continuous line) during a followup period of 5 years. B. Percentage of individuals taking glucocorticoid therapy in the group with severe gout (dashed line) and the group with non-severe gout (continuous line) before baseline (B) and during a followup period of 5 years.

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(Table 2). Although the study was performed in a dynamic cohort, in which individuals are recruited and leave the study at different times, all individuals included in the study could have been followed up for 5 years at the time we analyzed the study data. However, a high proportion of patients were lost to followup during the study. In the first year, 254 patients were in the study (59%). Of those, 118 had severe gout (47%) and 136 had non-severe gout (53%). In the second year, 189 patients were in the study (44%). Of those, 89 had severe gout (46%) and 100 had non-severe gout (54%). In the third year, 131 patients were in the study (37%). Of those, 62 had severe gout (47%) and 69 had non-severe gout (53%). In the fourth year, 81 patients remained in the study (23%). Of those, 36 had severe gout (45%) and 45 had non-severe gout (55%). In the fifth year, only 40 patients remained in the study (18%). Of those, 19 had severe gout (48%) and 21 had non-severe gout (55%). The mean followup was 27.6 ± 20.3 months. The median followup was 30 months (IQR 12–36).

Fixed pigmented erythema and rash were observed in 5% of the patients. One patient had a severe cutaneous adverse reaction to allopurinol. To our knowledge, 11 patients died after a followup period of 5 years. Six of those died in the first year; 2 died in the second year; 1 died in the third year; and 2 died in the fourth year.

TU levels during followup. TU < 6 mg/dl was achieved in 50–70% of the patients followed for 3–5 years. Fewer than 50% of patients achieved TU < 5 mg/dl during 5 years of followup. There were no significant differences in most percentages of SU 6 mg/dl or 5 mg/dl between severe gout versus non-severe gout patients (Figure 2A and 2B). Nadir urate levels were achieved after 36-48 months of followup. However, this tendency was reversed in subsequent assessments.

Gout remission during followup. After 1 year of followup, 9.1% of the patients were in remission. After 2 years, 30% of the patients were in remission, and after 3 years, 28% were in remission. A higher proportion of patients achieved remission after 4 years (39%), but assessments were performed in decreasing numbers of patients owing to loss to followup (Figure 3). Remission was observed in 28% of the patients after 5 years. Because remission criteria involve the absence of tophi, it was hard to achieve in patients with tophaceous gout. In fact, none of the patients with severe gout achieved remission.

DISCUSSION

Our study was aimed at determining the proportion of patients achieving TU levels defined as < 6 mg/dl for patients with non-severe gout and < 5 mg/dl for patients with severe gout, as well as the proportion of patients achieving remission after 5 years of followup. Although both groups improved significantly in all clinical outcomes, target SU and remission were difficult to achieve. Non-severe gout patients were closer to TU values, but no significant differences were observed across the study in percentages of severe gout versus non-severe gout patients achieving TU 6 mg/dl or 5 mg/dl. Even though patients with severe gout had clinical data of higher structural damage and received higher allopurinol doses, they achieved similar levels of SU. Although baseline SU levels in patients with severe gout were slightly higher than those found in patients with non-severe gout, severe gout is not limited to elevated SU values. It usually involves polyarticular flares, extensive tophaceous deposits, joint damage, and musculoskeletal disability. Severe gout represents neglected disease that has been untreated or insufficiently managed for many years[2].

The proportion of patients with non-severe gout achieving

Table 2. OMERACT domains for gout during followup.

Variables	Baseline	6 Mos	12 Mos	24 Mos	36 Mos	48 Mos	60 Mos
Severe gout							
Flares per year	9.14 (14.1)*	1.54 (8.04)	0.56 (1.5)	0.18 (0.45)	0.27 (0.78)	0.36 (0.85)*	0.68 (1.6)
ITS, cm	7.5 (3.5)*	7.3 (3.6)*	6.7 (3.9)*	6.8 (3.5)*	6.1 (3.7)*	5.5 (2.6)	6.32 (2.5)*
Pain-VAS	5.5 (2.9)*	4.3 (2.9)*	3.6 (2.6)*	2.8 (2.4)*	2.9 (2.6)*	1.6 (2.4)	3.1 (3.2)
HAQ	0.72 (0.36)*	0.65 (1.8)*	0.41 (0.50)*	0.29 (0.40)*	0.45 (0.05)*	0.22 (0.34)	0.53 (1.4)
SU, mg/dl	8.3 (2.3)	7.9 (7.7)	6.8 (1.9)	6.1 (1.9)	5.9 (2.1)	5.7 (2.1)	6.5 (2.2)
PtGA-VAS	4.6 (2.8)*	3.9 (3.0)*	3.3 (2.7)*	3.0 (2.5)	2.9 (2.8)	1.3 (2.1)	2.9 (2.8)
Non-severe gout							
Flares per year	5.38 (7.5)	0.56 (1.21)	0.40 (2.1)	0.30 (0.74)	0.18 (0.76)	0.83 (4.11)	0.57 (2.4)
ITS, cm	4.1 (2.5)	3.7 (2.06)	3.6 (2.4)	3.5 (2.1)	3.5 (1.9)	4.5 (4.2)	3.8 (2.0)
Pain-VAS	4.2 (3.2)	2.9 (2.8)	2.7 (2.7)	2.0 (2.7)	1.8 (2.4)	2.4 (3.0)	2.2 (2.7)
HAQ	0.35 (0.48)	0.20 (0.31)	0.17 (0.30)	0.17 (0.38)	0.42 (0.05)	0.23 (0.45)	0.16 (0.27)
SU, mg/dl	8.0 (2.1)	7.1 (4.7)	6.5 (1.9)	6.4 (2.1)	5.9 (1.7)	6.2 (1.8)	6.5 (2.1)
PtGA-VAS	3.4 (2.9)	2.7 (2.7)	2.6 (2.7)	2.3 (2.7)	2.2 (2.7)	2.5 (2.9)	2.5 (2.7)

Mean values (SD) are given for all variables. * Significant differences compared with values of the non-severe gout group. OMERACT: Outcome Measures in Rheumatology; ITS: index tophus size (length in cm of the longest axis of the biggest accessible tophus); Pain-VAS: visual analog scale for pain level; HAQ: Health Assessment Questionnaire score adapted for gout; SU: serum urate; PtGA-VAS: VAS for patient's global assessment.

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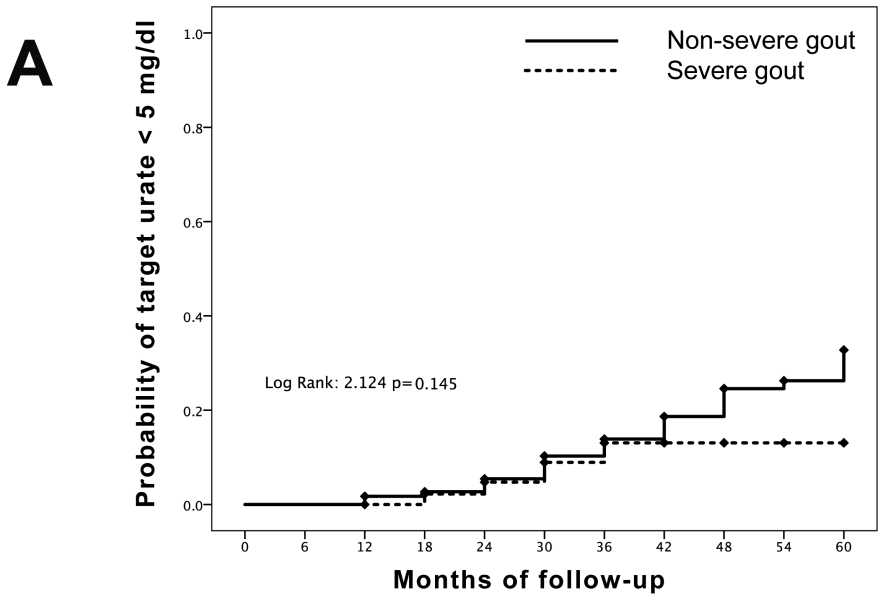

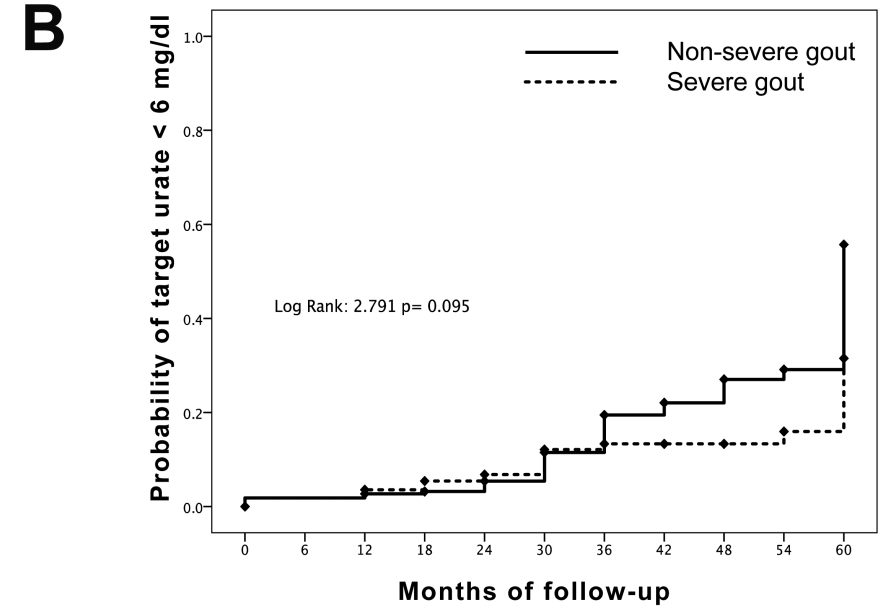

Number at risk

Severe gout	221	118	89	62	36	19
Non-severe gout	279	136	100	69	45	21

Figure 2. Kaplan-Meier curves for the time to target urate level. A. Kaplan-Meier survival curves for the time to target urate < 5 mg/dl of the group with severe gout (dashed line) and the group with non-severe gout (continuous line) during a followup period of 5 years. B. Kaplan-Meier survival curves for the time to target urate < 6 mg/dl of the group with severe gout (dashed line) and the group with non-severe gout (continuous line) during a followup period of 5 years.

remission increased during followup. In contrast, none of the patients with severe gout achieved remission. Remission criteria are demanding and strict for patients with severe gout. The main obstacles for remission found here were the number and size of tophi, the high percentage of patients lost to followup, and poor medication adherence.

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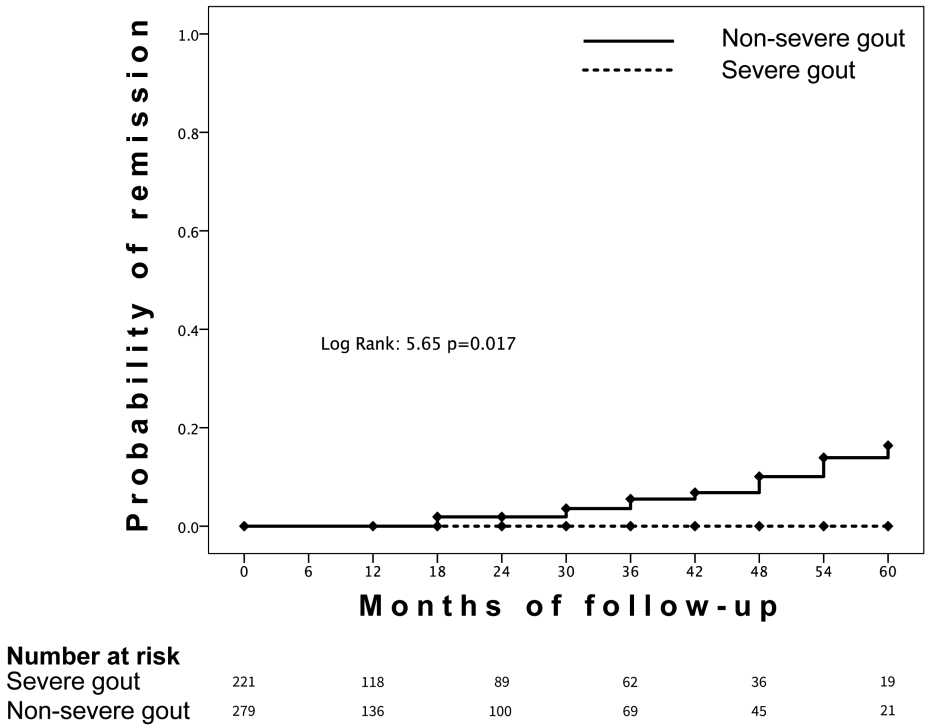

Figure 3. Kaplan-Meier curves for the time to remission. Kaplan-Meier survival curves for the time to remission of the group with severe gout (dashed line) and the group with non-severe gout (continuous line) during a followup period of 5 years.

Gout clinical management is based on the reduction of SU levels. An independent and robust association of target SU and allopurinol treatment adherence was previously reported in patients with gout; modifiable factors considered important for optimizing disease treatment outcomes include allopurinol dose escalation, treatment adherence, rheumatology referral, and concomitant medication use[21]. Poor medication adherence in patients with gout has been consistently described[22]. In a large, multicentric, international clinical trial it was recently reported that the trial regimen was discontinued in 56.6% of patients, and 45.0% discontinued followup[23]. But it should be considered that patient education and lifestyle advice may improve medication adherence and increase the proportion of patients achieving target SU levels[24]. In fact, nurse-led care, including providing patients with individualized information and engaging with them during care, along with a strategy of treat-to-target urate-lowering therapy, resulted in very high treatment uptake and adherence[25]. Moreover, patient-centered outcomes, such as flare frequency, tophi, and quality of life were substantially improved. However, this care model might not suit countries with less established nurse-led care, in which overworked practice-based nurses usually participate in clinical studies.

An important limitation of this and other gout cohort studies is the elevated proportion of patients lost to followup. The selection bias due to loss to followup, also known as informative censoring, represents a threat to the internal validity of estimates derived from cohort studies[26]. One year after baseline assessment, when our definition of remission involving SU < 6 mg/dl and absence of tophus and flares during at least 12 months of followup would be applicable for the first time, a high proportion of patients had already been lost to followup. We previously reported that after initiation of conventional treatment, patients with gout have a significant improvement at 6 and 12 months in most OMERACT domains for chronic gout. Greater improvement was observed in flares, index tophus size, pain, general health assessment, and HAQ score[27]. Thus, in the absence of flares, numerous patients are lost to followup because they feel healthy or they want to avoid labor absenteeism. Understanding the reasons and the outcomes of patients lost to followup in clinical practice is essential for the design of retention interventions. The reasons for losses and the outcomes may differ across cultural settings, types of diseases, and socioeconomic and educational levels. Sociostructural factors (e.g., lack of transportation or money and work/childcare responsibilities) have been reported as relevant reasons for loss to followup in patients with other chronic diseases living in developing countries. Outcomes among the lost are heterogeneous, but deaths and transfers to other clinics are common[28].

Another limitation of our study is that it was conducted in

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a large reference hospital in Mexico City, and this represents a potential source of referral bias affecting the generalizability of study results. Patients attending this hospital are from low socioeconomic backgrounds. Individuals with severe disease are more frequently sent to our gout clinic. It should be considered that patients with higher socioeconomic status may present less severe disease. Though our results are not generalizable to more compliant groups in developed countries, they may be extrapolated to populations with gout living in several developing countries such as Philippines[29]. It should also be considered that a limited number of patients declined to participate in the study because of a lack of time, and a few others were not invited to participate because they had a severe, life-threatening associated disease at their initial visit to our department. In both instances, a selection bias might have been introduced.

The self-prescription of GC by some patients may represent another study limitation, because these drugs interfere with the evaluation of the number of flares. Here we found that the use of self-prescribed GC was particularly higher in patients with severe gout. The causal relation of GC and severe gout remains to be elucidated, but we previously reported that longterm use of self-prescribed GC is associated with intradermal tophi and more severe disease[30]. The use of GC by patients with rheumatic disorders before attending rheumatology departments is common in developing countries. Initial prescriptions and recommendations usually come from general practitioners, non-rheumatologist specialists, and less frequently from lay persons. After that, patients may purchase GC without medical prescription[31]. In fact, most medications may be purchased without medical prescription in India, Brazil, and all over Latin America[32,33,34,35].

In the patients with severe gout studied here, target SU level was hard to achieve and remission was not possible. Gout is considered a reversible crystal deposition disease, as long as a timely diagnosis, adequate treatment, and appropriate referral to rheumatology departments are provided to affected individuals. In addition, effective gout patient education programs are critical to ensure treatment adherence, lifestyle changes, and continuity of medical care.

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