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ORIGINAL RESEARCH

Treatment with Allopurinol is Associated with Lower Risk of Acute Kidney Injury in Patients with Gout: A Retrospective Analysis of a Nested Cohort

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ABSTRACT

Introduction: Gout is characterized by recurrent episodes of acute inflammation of joint structures, called gout flares, and flares are commonly treated with nonsteroidal anti-inflammatory drugs (NSAIDs). The objective of the study was to evaluate risk factors associated with acute kidney injury (AKI) attributed to NSAIDs in a cohort of patients who were exposed to NSAIDs to treat gout flares prior to urate-lowering therapy.

Methods: Retrospective analysis of a nested cohort of 983 gout patients in whom general variables (age, gender, renal function, ethanol intake, hypertension, hyperlipidemia, diabetes, vascular events, diuretic use) and also variables related to gout and severity of gout (serum urate levels, number for flares per year, presence of tophi, joint distribution, X-ray involvement, previous urate-lowering therapy) were available for analysis. Outcomes considered were loss of renal function attributed to NSAID prescription following the RIFLE classification for (risk, injury, and failure) for acute renal events. Variables associated with increased risk in Kaplan–Meier survival analysis were tested with multivariable Cox survival analysis, using time from onset of gout to the event as time exposed to NSAIDs.

Results: Of 983 patients, 55 (5.6%) experienced AKI; the number of flares in the year previous to the renal event and polyarticular joint distribution were associated with higher risk of renal events. Other variables previously described in the literature, such as previous chronic renal disease, use of diuretics, and presence of previous vascular events, were also independently associated with increased risk of AKI. Interestingly, patients who had been previously prescribed allopurinol showed a lower risk of acute renal events.

Conclusion: In addition to classic risk factors, the number of flares and extensive joint distribution were associated with higher risk for renal injury in patients with gout, while previous prescription of allopurinol was associated with lower risk.

Keywords: Adverse events; Chronic gout; Gout; Kidney; NSAID

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INTRODUCTION

Gout is characterized by the development of recurrent episodes of acute inflammation (flares) of joint structures, commonly named as gout

flares or gout attacks [1]. Flares in patients with gout are most commonly treated with nonsteroidal anti-inflammatory drugs (NSAIDs), and the highest labeled doses are commonly recommended [2]. Among the serious adverse events associated with the use of NSAIDs [3], renal ones—including acute kidney injury (AKI) and permanent loss of renal function [4]—are not uncommon, especially in patients at risk [5].

Variables specifically related to gout severity, such as joint distribution, the number of episodes of inflammation, or presence of tophaceous deposition, may be associated with a more frequent use of NSAIDs, and therefore to NSAID-related adverse events. Unfortunately, these variables are not available from databases in former publications [6]. We investigated risk factors for developing AKI in a large cohort of patients with gout in whom gout-specific variables were available.

METHODS

This was a retrospective analysis of data from a cohort of patients with gout who visited our university hospital, which is responsible for treating a population of half a million, from September 1992 to September 2013. At entrance in the follow-up cohort, general data, biometrics, renal function, cardiovascular risk factors, and previous complications due to medications for gout were incorporated into the dataset along with specific data related to gout. The dataset capture was approved by the local ethics committee and written consent provided by the patients.

Outcomes considered were the presence of a physician-based diagnosis history of suspected or confirmed AKI attributed to NSAIDs in the clinical file of the patient by a physician. The files of the patients with an entry in the dataset related to AKI were reviewed to ascertain the endpoints. For AKI, RIFLE classification was used, and at least a 25% decrease in estimated clearance of creatinine with MDRD formula was needed to fulfill criteria for risk, 50% for injury, and 75% for failure [7].

Exploratory variables included age, gender, body mass index (BMI), clinically significant chronic kidney disease (CKD, defined as glomerular filtration rate <60 ml/min), use of diuretics, diabetes, hypertension, hyperlipidemia, previous vascular events, and previous renal lithiasis. Gout-specific variables included were time from onset of gout, number of joints ever involved during the natural course of the disease (monoarticular, oligoarticular, or polyarticular gout), presence of X-ray abnormalities related to gout, presence of subcutaneous tophi, previous urate-lowering treatment (ULT), number of episodes of acute inflammation (flares) of gout in the year previous to consultation, and serum urate at baseline.

Continuous variables are expressed as mean ± SD. Time from onset of gout was considered as time exposed to NSAIDs for analysis. Kaplan–Meier estimates of survival using a log-rank test were used to initially identify those variables associated with the outcome (AKI). Variables found to have a possible statistical association ($p < 0.20$) with AKI in the bivariable analysis ($p < 0.20$) were selected for a multivariate Cox proportional hazard regression analysis using a stepwise model, so that the variable showing the highest non-significant p statistic at every step was withdrawn from the multivariate model until all remaining variables showed statistical significance ($p < 0.05$). Hazard ratios (HR) and 95% confidence intervals (95% CI) were obtained from bivariable and multivariate models.

The robustness of the models was checked with partial residuals plots to support the hypothesis of proportional hazards. For numerical variables, the proportional risk hypothesis was tested categorizing variables into quartiles. Statistical analyses were run in the statistical package SPSS v19.0.

The cohort recruitment and follow-up were approved by the Ethics and Investigation Board at Cruces University Hospital and written consent provided by the patients. This study did not include any new intervention.

RESULTS

Twenty-one patients were excluded because their flares had always been treated with colchicine or corticosteroids and they were never exposed to NSAIDs for gout flares. A total of 983

Table 1 General characteristics of the cohort and patients with placebo and AKI

	All $N = 983$	AKI (−) $N = 928$	AKI (+) $N = 55$	p
Age (years)	60.1 ± 13.1	59.7 ± 13.1	68.2 ± 12.1	<0.001
BMI (kg/m^2)	27.9 ± 3.9	27.9 ± 3.9	27.6 ± 4.0	0.562
Time from onset (years)	6.8 ± 7.1	6.8 ± 7.1	7.9 ± 7.4	0.266
Serum urate (mg/dl)	8.98 ± 1.41	8.96 ± 1.39	9.38 ± 1.70	0.065
Flares (previous years)	3.6 ± 3.8	3.5 ± 3.6	5.5 ± 5.6	0.012
GFR (ml/min/1.73 m^2)	88 ± 54	90 ± 54	57 ± 38	<0.001
Male/female	913/70	862/66	50/5	0.582
Hypertension (%)	46.8	45.6	74.5	<0.001
Diuretics (%)	27.3	24.3	56.4	<0.001
CKD stage <2 (%)	23.6	21.6	56.5	<0.001
Renal lithiasis (%)	9.2	9.7	0	0.034
Diabetes (%)	20.0	19.4	30.9	0.035
Hyperlipidemia (%)	45.2	45.4	41.2	0.634
Previous vascular event (%)	29.7	27.8	61.8	<0.001
Polyarticular	35.7	34.3	65.9	<0.001
Tophi	32.4	31.5	49.1	0.007
Concomitant allopurinol	39.8	39.4	25.4	0.155

patients were included for analysis and for 774 (78.6%) of these the diagnosis was based on urate crystal observation in synovial fluid or samples aspirated from tophi. Three cases with prerenal kidney injury related to gastrointestinal bleeding were not adjudicated as AKI.

Time from onset of gout was 6.8 ± 7.1 years (median 4; interquartile range 2–10), exposure to NSAIDs being 6684 patients/year. General characteristics of the patients are shown in Table 1. A total of 39% (385/983) of the patients had been on urate-lowering drugs, all but one of them with allopurinol (43% on <300 mg/day, 57% on ≥300 mg/day).

The following AKI events occurred: risk of renal dysfunction, 31 (3.15%); injury to the kidney, 13 (1.32%); failure of kidney function, 11 (1.12%), with a total of 55 events (5.6% cumulative incidence), 0.82 events per 100 patient-year exposure.

Variables independently associated with increased risk of AKI in Kaplan–Meier, log-rank bivariable survival analysis were age, gender, hypertension, diabetes, previous CKD, previous lithiasis, diuretic use, number of flares, polyarticular distribution of joint involvement, and previous vascular event. Cox regression multivariate analysis showed that CKD, diuretic use, previous vascular event, polyarticular distribution, number of episodes of inflammation in the previous year, and absence of concomitant ULT were independently associated with increased risk (Table 2).

Overall, the concomitant use of allopurinol was associated with a reduction in the risk of AKI. An analysis to evaluate whether the reduction of risk was associated with prescribed doses of allopurinol did not reach statistical significance, as all patients had been prescribed doses equal to or lower than 300 mg/day (data not shown).

Table 2 Risk ratios (95% confidence interval limits) for variables included in Cox survival analysis

	AKI, uncorrected	AKI, corrected	*p*
Diabetes	1.127 (0.611–2.078)	0.996 (0.541–1.831)	0.996
Age (years)	1.003 (0.977–1.030)	1.002 (0.976–1.029)	0.876
Gender (male)	0.551 (0.190–1.601)	0.593 (0.205–1.761)	0.335
Hypertension	1.396 (0.621–3.141)	1.448 (0.663–3.163)	0.353
Diuretic use	1.963 (0.988–3.898)	**2.168 (1.130–4.161)**	**0.020**
CKD stage <2	2.755 (1.435–5.286)	**2.695 (1.404–5.172)**	**0.003**
Previous vascular event	2.173 (1.708–4.383)	**2.453 (1.259–4.782)**	**0.008**
Polyarticular	3.560 (1.233–10.282)	**3.90 (1.358–11.216)**	**0.011**
Flares (>2 per year)	2.489 (1.194–5.187)	**2.723 (1.030–5.693)**	**0.008**
Not on allopurinol	3.634 (1.880–7.022)	**3.921 (2.056–7.476)**	**0.000**

Statistically significant variables after correction are shown in bold

DISCUSSION

Although gout is a well-known disease, a minority of patients receive adequate advice and treatment [8]. Even a majority of patients with long-standing gout do not receive ULT [9], and half of those who receive them do not reach therapeutic plasma urate levels even when treated [10]. Although proper treatment of hyperuricemia to target therapeutic serum urate levels is associated with a decrease in the number of flares [11], persistence of hyperuricemia is associated with an increase in the number and severity of flares [12]. So far, the long-term control of hyperuricemia and the subsequent avoidance of NSAIDs have been associated with improvement in renal function, the highest impact observed in patients with CKD [13]. In addition, treatment of hyperuricemia of gout may be considered cost-effective in patients at high risk of developing adverse events due to the use of NSAIDs [14].

The number of flares and the presence of polyarticular joint distribution were associated with higher risk of AKI complications in our patients. The number of flares and polyarticular distribution could be considered as surrogates of the use of NSAIDs, commonly prescribed at high dose for gout flares. The clinical implications for such findings are that recurrence of flares should be avoided by correct implementation of ULT in patients with gout [15, 16], prescribing adequate prophylaxis to patients starting ULT [17], and a slow step-up dosing of urate-lowering drugs should be considered [14] to minimize the risk of flares in patients with renal function impairment.

The use of diuretics, previous vascular events, and no previous treatment with urate-lowering drugs were associated with risk of developing AKI. Cyclooxygenase inhibition causes marked impairment of renal function in elderly patients, especially if treated with diuretics or ACE inhibitors [18]. The rate of adverse events caused by NSAIDs that required hospitalization is increased in patients on ACE inhibitors or diuretics, additional comorbidities highly influencing the risk [5]. Although short-term use of NSAIDs seems not to have a clinically relevant impact on renal function in patients with previous normal renal function [19], even if administered at high doses [20], the presence of CKD is considered a risk factor for renal injury due to NSAIDs [21], and it has been found to be associated with AKI in patients with gout [6].

Interestingly, patients who had concomitant allopurinol prescription were at lower risk of

developing AKI than patients not treated. The impact of allopurinol treatment on renal function is debated, but some trials have shown treatment with allopurinol to have a beneficial effect on endothelial function and glomerular filtration [22] even regardless of the impact on serum urate levels [23]. Although not labelled in most countries for such an indication, early treatment of hyperuricemia in patients with CKD is suggested by some authors [16].

The strength of this study lies in the availability of variables associated with the severity of gout involvement such as the number of flares, which may be a surrogate for the number of times high-dose NSAIDs are used, and clinical variables of chronicity of gout such as polyarticular joint distribution and tophaceous deposition, which may reflect a more frequent use of low-dose NSAIDs or analgesics apart from the flares. Limitations to the results include that some variables known to be risk factors for AKI, such as ACE inhibitors [18], were not included in the protocol of the cohort. Also, the variable for previous vascular event was heterogeneous, as it included patients with acute and chronic heart failure, stroke or myocardial infarction, the presence of previous chronic heart failure being the most likely cause associated with AKI [21], but no further data were available for analysis. The incidence of AKI may also have been underestimated, as data regarding renal function after flares was not always available and therefore capture of adverse events was missed. The highest doses of allopurinol were not associated with a reduction of the risk of AKI, but the number of patients was relatively small and no data on the impact of allopurinol treatment on serum urate levels was incorporated, as most patients did not have previous controls, as reported previously in other studies [9].

CONCLUSIONS

Along with known risk factors for renal adverse events—such as CKD, previous vascular event, and diuretic use—variables related to gout severity, such as the number of acute episodes of inflammation and polyarticular distribution, were associated with such adverse events. Concomitant use of allopurinol was associated with a reduction of the risk, but we cannot establish a relationship with doses or serum urate levels because of the lack of sufficient numbers of patients and data. Appropriate treatment of hyperuricemia of gout should be implemented in any patient with a certain diagnosis of gout, but especially in patients with comorbidities and higher risk of developing adverse events to NSAIDs.

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Compliance with Ethics Guidelines. The cohort recruitment and follow-up were approved by the Ethics and Investigation Board at Cruces University Hospital and written consent provided by the patients. This study did not include any new intervention.

Data Availability. The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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