Gout Prophylaxis Evaluated According to the 2012 American College of Rheumatology Guidelines: Analysis from the CORRONA Gout Registry

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ABSTRACT. ***Objective.*** To analyze prophylaxis using the CORRONA (COnsortium of Rheumatology Researchers Of North America) Gout Registry according to the American College of Rheumatology (ACR) guidelines, and to evaluate whether differences in disease characteristics influenced prophylaxis.

Methods. All patients with gout in the CORRONA Gout Registry between November 1, 2012, and November 26, 2013, were included. They were divided into 2 groups: "receiving prophylaxis" versus "not receiving prophylaxis" at the time of enrollment. Patients having a flare at time of visit were excluded. Descriptive statistics and multivariable logistic regression models were performed to evaluate the factors associated with prophylaxis.

Results. There were 1049 patients with gout available for analysis. There were 441 patients (42%) receiving prophylaxis and 608 (58%) not receiving prophylaxis. The most common drugs used for prophylaxis were colchicine (78%) and nonsteroidal antiinflammatory drugs (32%). Prophylaxis drug combination was used by 45 patients (10.2%). Patients in the "receiving prophylaxis" group were more likely to have a gout duration of ≤ 1 year ($n = 68$, $p < 0.001$), ≥ 1 flare in the year previous to enrollment ($p < 0.001$), ≥ 1 healthcare uses in the last year [Emergency Department ($p = 0.029$); outpatient visit to primary care, rheumatologist, or urgent care clinic ($p < 0.001$)], have tophi ($p < 0.001$), report pain > 3 ($p = 0.001$), and have disease activity > 10 ($p < 0.001$) compared with patients in the "not receiving prophylaxis" group.

Conclusion. Forty-two percent of patients with gout in the CORRONA Gout Registry were receiving prophylaxis. Prophylaxis was significantly more common in patients with a higher disease burden and activity, which is in agreement with the ACR guidelines. Our study highlights disease characteristics influencing prophylaxis and furthers our knowledge on current use of flare prophylaxis. (First Release March 15 2016; J Rheumatol 2016;43:924–30; doi:10.3899/jrheum.150345)

Key Indexing Terms:
GOUT FLARE PROPHYLAXIS

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Gout is the most common inflammatory arthritis in men and older women, affecting an estimated 8.3 million adults in the United States[1]. The management of gout is focused on treating pain and inflammation associated with acute flares and preventing further acute flares, as well as monosodium urate (MSU) crystal deposition[2,3,4].

A challenge associated with the successful management of gout is the increase in acute gout flares during the first months after initiation of urate-lowering therapies (ULT) as a result of rapid changes in serum urate (SU) levels[5]. This increase in flare frequency has been observed regardless of the choice of ULT (e.g., allopurinol, febuxostat, probenecid, pegloticase)[6,7] and has been linked to suboptimal patient adherence to ULT[4,8,9]. Failure to adequately control gout flares during the initiation of ULT can result in suboptimal patient adherence to treatment[5,10,11].

The exact mechanism by which ULT trigger acute flares is not well understood. It has been suggested that the increased flare rate may result from alterations in the chemical and/or physical state of preexisting MSU crystals when ULT induce rapid changes in SU levels[12]. Thus, super-

ficial MSU crystals become solubilized, exposing uncoated (i.e., lacking protein coat) MSU crystals to monocytes and synoviocytes, stimulating activation of the NALP-3 inflammasome and increasing the expression of proinflammatory cytokines such as interleukin (IL)-1[13].

According to the 2012 American College of Rheumatology (ACR) guidelines[14], antiinflammatory drugs for flare prophylaxis are recommended when ULT are initiated and should be continued if there is continuing gout disease activity and/or the SU target has not been achieved. The guidelines[14] recommend low-dose colchicine (0.5 mg or 0.6 mg orally) once or twice daily. Colchicine is considered the standard of care for flare prophylaxis during the initiation of ULT, and is currently the only US Food and Drug Administration–approved therapy for gout flare prophylaxis. Other options were giving nonsteroidal antiinflammatory drugs (NSAID) with a proton pump inhibitor, low-dose corticosteroids [prednisone (PRED) ≤ 10 mg/d], or IL-1 inhibitors (anakinra in United States and Europe, and canakinumab in Europe). Recommended was the initiation of these drugs when starting ULT. Duration of prophylaxis was recommended for ≥ 6 months: 3 months posttarget SU reached (when no tophi) and 6 months posttarget SU reached when there were resolution tophi.

Management of gout includes treating chronic hyperuricemia and reducing the MSU crystal burden, as well as treating and preventing flares. Despite the current treatment recommendations, we suspect that in practice, antiinflammatory prophylaxis is not being prescribed regularly. Flares occur mainly during the first months, because of tophus mobilization and the rapid changes in SU. Our aim was to assess the frequency of gout flare prophylaxis, and record what drugs are commonly used for prophylaxis and if they are used according to the 2012 ACR recommendations[14]. In addition, we wanted to assess whether there were differences in disease characteristics such as the number of flares, pain in the past week, disease activity, medications used, and doses, as well as adverse events and hospitalizations in patients receiving prophylaxis compared with those who were not receiving prophylaxis.

MATERIALS AND METHODS

Data source and population. The COnsortium of Rheumatology Researchers Of North America (CORRONA) is a prospective observational cohort of patients with arthritis who are enrolled by participating rheumatologists in both academic and private practice sites; the details have been previously published[15,16].

For the Gout Registry, rheumatologists were asked to enroll patients aged 21 years and older who met the criteria for the diagnosis of gout based on the ACR criteria. Data were collected from patients and their treating rheumatologists using standard clinical research forms. Information collected included demographics, comorbid conditions, gout presentation, disease severity and activity, family history of gout, body mass index (BMI), dietary intake over the past week, use of medications that can raise SU level (e.g., diuretics), use of medications for acute gouty inflammation (NSAID, colchicine, corticosteroids, and anakinra), and ULT including uricosurics, xanthine oxidase inhibitors, and recombinant uricase (pegloticase). Documentation included physician's examination findings of tophi and inflamed joints, physician's and patient's global assessments of disease activity, patient's assessment of pain, the Health Assessment Questionnaire (HAQ) assessing physical function, and serum uric acid levels from laboratory tests obtained within 10 days of the clinical encounter (these data were not mandated by the study protocol). Patients reported the number of days in the past 3 months they were unable to perform their usual activity. Healthcare use data were gathered, including gout hospitalizations within the last 3 years as well as Emergency Room (ER) and/or outpatient visits in the past 12 months for gout flares. Additionally, patients reported how many flares they managed themselves without seeing a healthcare professional.

There were 1049 patient visits, aged 18 and older, entered in the CORRONA Gout Registry database for this population between November 1, 2012, and November 26, 2013, and available for analysis. There are 34 rheumatology practices participating in the registry with > 80 rheumatologists involved, of whom 88% are in private practice. There are no disease activity requirements or comorbidity exclusion criteria. Approvals for data collection and analyses were obtained for academic and private practice sites from local and central institutional review boards, respectively.

Measures and data collection. We identified patients receiving prophylaxis by using the physician's report of medication prescription. Among the data elements collected in the registry relevant to our study, there were physician's examination findings of tophi and inflamed joints, physician's and patient's global assessments of disease activity, patient's assessment of pain, the HAQ assessing physical function, and SU levels. SU data were recorded from laboratory tests obtained within 10 days of the clinical encounter. Chronic kidney disease (CKD) is defined as the presence of kidney damage, or a decreased level of kidney function, for a period of 3 months or more. Glomerular filtration rate (GFR) was calculated using the Modification of Diet in Renal Disease. CKD can be divided into 5 stages, based on GFR: normal (stage 1), mild CKD (stage 2) 60–89 ml/min, moderate CKD (stage 3) 30–59 ml/min, severe CKD (stage 4) 15–29 ml/min, and endstage renal disease (stage 5) < 15ml/min. Collection of laboratory data, however, was not mandated by the study protocol.

Prophylaxis medication exposure cohorts. Patients were categorized based on the use of chronic suppressive therapy and dichotomized into 2 groups: "receiving prophylaxis" versus "not receiving prophylaxis." Patients with gout were considered in the "receiving prophylaxis" group if at the time of enrollment they were receiving colchicine, an NSAID, PRED (≤ 10 mg), or IL-1 inhibitors (anakinra or canakinumab), and were reported by the treating rheumatologist to not have a flare. Patients in the "not receiving prophylaxis" group included patients receiving PRED at a dose of > 10 mg or receiving no acute gout medications. Patients having a flare at time of visit were excluded from our study.

Covariates for comparison. We compared patients "receiving prophylaxis" to those "not receiving prophylaxis" based on baseline characteristics at the time of enrollment. These included sociodemographic characteristics such as age, sex, race, ethnicity, education, work status, insurance status, and marital status. BMI was evaluated and compared based on the World Health Organization categories of underweight (< 18.5), normal (18.5–24.9), overweight (25–29.9), obesity class 1 (30–34.9), and obesity class II/III (35+). Gout characteristics based on physician documentation included age at gout onset, duration of gout, presence of tophi, comorbid conditions, hospitalizations for gout, and medications (both acute and chronic medications). Patient-reported variables included disease activity [0–100 on a visual analog scale (VAS)], pain (0–100 on a VAS), number of gouty flares in the prior 12 months, and healthcare use for gout. Laboratory data included serum uric acid level, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR).

Statistical analysis. The Student 2-sample t test (continuous variables) and chi-square test (categorical variables) were used to compare factors between the "receiving prophylaxis" and "not receiving prophylaxis" groups. If cell sizes were small (< 5 found in a cell), the Fisher's exact test was used in place of the chi-square test, and this is indicated in the tables.

Logistic regression was used to estimate the association of factors with prophylaxis treatment. First, each factor of interest was evaluated in a univariable model. Those factors with a resulting p value < 0.20 were further evaluated simultaneously in a multivariable logistic model. Prior to the multivariable model, the possible existence of multicollinearity among the predictor variables in the multivariable model was evaluated. Variables found to be pairwise correlated at a level > 0.20 or –0.20 were flagged. These flagged pairs included the number of flare attacks and pain, number of flare attacks and disease activity, and pain and disease activity. Because a patient would not be receiving joint therapy of allopurinol and febuxostat, the following categorical variables were created: not receiving either drug (reference), allopurinol 50–200 mg, allopurinol > 200–300 mg, allopurinol > 300 mg, febuxostat 40 mg, and febuxostat 80 mg/other.

Two final multivariable logistic models, 1 each for the number of flare attacks and disease activity, were fit. Each of the 2 models included marital status, years of gout, hospitalization in the last 3 years, serum acid level, combined allopurinol and febuxostat use, and presence of tophi because these were significant at the 0.2 level in univariable analyses. Sex and age at enrollment were also included in the final models. To account for the clustering of patients by physician, we evaluated the practice site as a random effect in the final multivariable model.

Because of the potentially small group sizes, we collapsed the categories for the following variables prior to inclusion in the regression models: race (white vs non-white), education (> 12 yrs vs ≤ 12 yrs), BMI categories (underweight/normal, overweight, and obese), work status (full/part-time vs others), marital status (single, married/partners, and others), adverse effect to any medication (allergy/side effect vs other), allopurinol (not receiving drug, 50–200 mg, > 200–300 mg, > 300 mg), febuxostat (not receiving drug, 40 mg, 80 mg/other), and probenecid (not receiving drug, 250–750 mg, 1000–2500 mg).

In addition, to avoid any modeling issues because of sparseness in the distributions of these continuous variables, the following continuous variables were dichotomized at the median of the "not receiving prophylaxis" group or as otherwise noted to have meaningful group comparisons in the final model: duration of gout (dichotomized as newly diagnosed ≤ 1 reference vs other, and median > 7 vs ≤ 7); number of flares in past year (> 1 vs ≤ 1); patient's reported pain (> 3 vs ≤ 2); disease activity (> 10 vs ≤ 9); healthcare use (no. visits) in the past 12 months to the ER (≥ 1 vs 0); outpatient visit to rheumatologist, primary care provider, or urgent care clinic (> 1 vs ≤ 1); no care (≥ 1 vs 0); CRP at first visit (≤ 0.42 mg/dl vs > 0.42); ESR at first visit (≤ 12 mm/h vs > 12); and SU at first visit (≥ 5 vs 5, and also ≥ 6 vs < 6).

RESULTS

One thousand forty-nine patients with gout were available for analysis in the CORRONA Gout Registry. There were 441 patients with gout (42%) who were receiving prophylaxis and 608 (58%) who were not receiving prophylaxis. Characteristics of patients with gout in the CORRONA Registry at the time of enrollment by prophylaxis group compared among the 2 groups are shown in Table 1. Disease characteristics of patients with gout in the CORRONA Registry at the time of enrollment by prophylaxis group compared among the 2 groups are shown in Table 2. The history of comorbid conditions, alcohol consumption, and other dietary factors at the time of enrollment by prophylaxis group are shown in Table 3.

Prophylaxis included colchicine (n = 345, 78%); NSAID (n = 140, 32%; ibuprofen, n = 56; indomethacin, n = 51; celecoxib, n = 44); PRED, n = 30 (7%); methylprednisolone, n = 4 (< 1%); and anakinra, n = 3 (< 1%). Prophylaxis drug combination was used by 45 patients (10.2%). Ninety-six percent of colchicine users were receiving 0.5 mg or 0.6 mg, and 53% were receiving a once-daily dosing. There were 918 patients (88%) receiving a ULT (allopurinol 79%, n = 735;

Table 1. Characteristics of gout patients in CORRONA registry at time of enrollment by prophylaxis group. P values are from the 2-sample Student t test for continuous variables and the chi-square test of association for categorical variables, except where indicated with an asterisk. Values are n (%) unless otherwise specified.

Characteristics	Receiving Prophylaxis, N = 441	Not Receiving Prophylaxis, N = 608	p
Sex, N_o	439	606	0.195
Male	355 (80.9)	470 (77.6)	
Age, yrs, N_o	441	608	
Mean ± SD	63.2 ± 13.7	63.7 ± 13.1	0.614
36–45	49 (11.1)	60 (9.9)	
46–55	67 (15.2)	94 (15.5)	
56–65	121 (27.4)	167 (27.5)	
66+	204 (46.3)	287 (47.2)	0.932
Race, N_o	441	608	
White	382 (86.6)	549 (90.3)	
African American	25 (5.7)	23 (3.8)	
Asian	15 (3.4)	13 (2.1)	
Other	19 (4.3)	23 (3.7)	0.253
Ethnicity, N_o	363	490	
Hispanic	5 (1.4)	9 (1.7)	0.787*
Education, yrs, N_o	434	598	
≤ 6	22 (5.1)	27 (4.5)	
7–12	143 (33.0)	204 (34.1)	
> 12	268 (61.8)	367 (61.4)	0.874
Work status, N_o	440	603	
Full-time	176 (40.0)	239 (39.6)	
Part-time	19 (4.3)	36 (6.0)	
Retired	200 (45.5)	271 (44.9)	
Other	45 (10.2)	57 (9.5)	0.603
Insurance, N_o**	441	608	
None	6 (1.4)	5 (< 1)	0.541*
Private	323 (73.2)	438 (72.0)	0.666
Medicare	193 (43.8)	269 (44.2)	0.877
Medicaid	0 (0.0)	0 (0.0)	—
Marital status, N_o	438	606	
Single	39 (8.9)	68 (11.2)	
Married	309 (70.6)	436 (72.0)	
Partnered	5 (1.1)	6 (1.0)	
Widowed	38 (8.7)	43 (7.1)	
Separated	3 (0.7)	9 (1.5)	
Divorced	44 (10.1)	44 (7.3)	0.303*
BMI, N_o	411	584	
Mean ± SD	32.3 ± 7.0	32.2 ± 6.8	0.782
Underweight, < 18.5	3 (0.7)	4 (0.7)	
Normal, 18.5–24.9	29 (7.1)	29 (7.1)	
Overweight, 25–29.9	141 (34.3)	141 (34.3)	
Obesity Class 1, 30–34.9	122 (29.7)	122 (29.7)	
Obesity Class 2/3, 35+	116 (28.2)	116 (28.2)	0.951*

* P values from Fisher's exact test. ** Sums may not add to 100% because of overlap in private and Medicare groups. N: total number of patients; N_o: number of patients with available data for each characteristic; n: number of patients with attribute out of N_o; %: percent of n out of N_o; CORRONA: COnsortium of Rheumatology Researchers Of North America; BMI: body mass index.

Table 2. Disease characteristics of patients with gout in CORRONA Registry at time of enrollment by the prophylaxis group. P values are from the 2-sample Student t test for continuous variables and the chi-square test of association for categorical variables, except where indicated with an asterisk. Values are n (%) unless otherwise specified.

Characteristics	Receiving Prophylaxis, N = 441	Not Receiving Prophylaxis, N = 608	p
Age of gout onset, yrs, N_o	434	606	0.163
Mean ± SD	54.0 ± 17.0	52.6 ± 15.6	
Duration of gout, yrs, N_o	434	606	0.005
Mean ± SD	9.3 ± 9.2	11.0 ± 10.0	
Newly diagnosed, ≤ 1 yr	68 (15.7)	52 (8.6)	< 0.001
Patient-reported disease activity, N_o	436	606	
Mean ± SD**	19.2 ± 23.8	12.3 ± 20.3	< 0.001
Patient-reported pain, N_o	435	606	
Mean ± SD**	16.3 ± 26.0	11.2 ± 21.4	0.001
Presence of tophi, N_o	441	608	
n (%)	116 (26.3)	103 (16.9)	< 0.001
Hospitalization last 3 yrs, N_o	441	608	
n (%)	13 (3.0)	10 (1.6)	0.155
Healthcare use, no. visits, in the past 12 mos, N_o	440	606	
Emergency room visits, mean ± SD	0.28 ± 0.93	0.17 ± 0.67	0.029
Outpatient visit to rheumatologist, primary care provider, or urgent care clinic, N_o	437	607	
Mean ± SD	1.66 ± 3.20	0.92 ± 1.87	< 0.001
No. flares, but did not seek care, N_o	436	606	
Mean ± SD	2.5 ± 6.1	1.3 ± 4.1	< 0.001
Serum uric acid, mg/dl, N_o	379	516	
Mean ± SD	6.2 ± 2.0	5.6 ± 1.7	< 0.001
Serum uric acid < 6	198 (52.2)	326 (63.2)	0.001
CRP, mg/dl, N_o	160	196	
Mean ± SD	1.10 ± 2.41	0.84 ± 1.83	0.232
ESR, mm/h, N_o	175	229	
Mean ± SD	21.6 ± 21.6	18.6 ± 19.6	0.145
CKD, N_o	200	284	
Mild, ≥ 60 ml/min	129 (64.5)	200 (70.4)	
Moderate, ≥ 30 and < 60 ml/min	66 (33.0)	66 (23.2)	
Severe, < 30 ml/min	5 (2.5)	18 (6.3)	0.016*

* P values from Fisher's exact test. ** Scale is 0 to 100. N: total number of patients; N_o: number of patients with available data for each characteristic; n: number of patients with attribute out of N_o; %: percent of n out of N_o; CORRONA: COnsortium of Rheumatology Researchers Of North America; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; CKD: chronic kidney disease.

febuxostat 16%, n = 162; probenecid < 1%, n = 17; and pegloticase < 1%, n = 7). Of the patients, 292 (67%) receiving prophylaxis had a disease duration of ≥ 1 year.

Within both subgroups not receiving/receiving ULT, stratified by patients receiving prophylaxis versus those not receiving prophylaxis, SU level was associated with ULT use: $p < 0.001$ within both groups (Table 4).

Of the 441 patients receiving prophylaxis, 200 (46%) had CKD reported (Table 2). Four patients with severe CKD [creatinine clearance (CrCl) < 30 ml/min] were receiving colchicine prophylaxis; 2 (50%) of them had their colchicine dose adjusted accordingly to 0.3 mg/day. NSAID were used for prophylaxis in patients with CKD: 17% of patients (56/329) with CKD stage 2 and 14% of patients (19/132) with CKD stage 3, and 4% of patients (1/23) with CKD stage 4 were receiving NSAID prophylaxis.

Patients in the "receiving prophylaxis" group were more likely to have a gout duration of ≤ 1 year (n = 68, $p < 0.001$), ≥ 1 flare in year previous to enrollment ($p < 0.001$), and ≥ 1 healthcare use in the last year (ER, $p = 0.029$; outpatient visit to primary care, rheumatologist, or urgent care clinic, $p < 0.001$; or ≥ 1 flare but did not seek care, $p < 0.001$) compared with patients in the "not receiving prophylaxis" group. In addition, patients in the "receiving prophylaxis" group were less likely to have SU < 6 mg/dl ($p < 0.001$) and more likely to have tophi ($p < 0.001$), report pain > 3 ($p = 0.001$), and have disease activity > 10 ($p < 0.001$) compared with patients in the "not receiving prophylaxis" group. Comorbidities did not have a significant effect on whether the patient was treated with prophylaxis.

Logistic regression was used to estimate the association of factors with prophylaxis treatment. First, each factor of

Table 3. History of comorbid conditions, alcohol consumption, and other dietary factors at time of enrollment by the prophylaxis group. P values are from the chi-square test of association, except where indicated with an asterisk. Values are n (%) unless otherwise specified.

Variables	Receiving Prophylaxis, N = 441	Not Receiving Prophylaxis, N = 608	p
Comorbid conditions			
History of DM, N_o	441	608	
n (%)	89 (20.2)	114 (18.8)	0.562
History of CVD, N_o	441	608	
At least 1 of the following	67 (15.2)	94 (15.5)	0.905
Acute coronary syndrome	3 (0.7)	8 (1.3)	0.374*
Coronary artery disease	48 (10.9)	69 (11.4)	0.843
Congestive heart failure	15 (3.4)	23 (3.8)	0.867
Myocardial infarction	15 (3.4)	29 (4.8)	0.275
Peripheral arterial disease	6 (1.4)	6 (1.0)	0.573*
History of HTN, N_o	441	608	0.213
n (%)	285 (64.6)	370 (60.1)	
History of kidney disease, N_o	441	608	
n (%)	29 (6.6)	36 (5.9)	0.664
History of nephrolithiasis, N_o	441	608	
n (%)	23 (5.2)	37 (6.1)	0.549
Alcohol consumption, daily			
Beer, drinks, N_o	424	578	
0	284 (67.0)	373 (64.5)	
1–2	67 (15.8)	85 (14.7)	
3+	73 (17.2)	120 (20.8)	0.366
Wine, glasses, N_o	417	575	
0	309 (74.1)	422 (73.4)	
1–2	58 (13.9)	99 (17.2)	
3+	50 (12.0)	54 (9.4)	0.197
Hard liquor, drinks, N_o	409	569	
0	324 (79.2)	461 (81.0)	
1–2	36 (8.8)	60 (10.5)	
3+	49 (12.0)	48 (8.4)	0.146

* P values from Fisher's exact test. N: total number of patients; N_o: number of patients with available data for each characteristic; n: number of patients with attribute out of N_o; %: percent of n out of N_o; DM: diabetes mellitus; CVD: cardiovascular disease; HTN: hypertension.

Table 4. SU Levels by ULT use stratified by patients receiving prophylaxis versus not receiving prophylaxis. P values are from the chi-square test of association. Values are n (%) unless otherwise specified.

Variables	Not Receiving ULT	Receiving ULT	p
Not receiving prophylaxis	N_o = 45	N_o = 471	
SU < 5 mg/dl	12 (27)	314 (67)	
SU ≥ 6 mg/dl	33 (73)	157 (33)	< 0.001
Receiving prophylaxis	N_o = 58	N_o = 321	
SU < 5 mg/dl	11 (19)	187 (58)	
SU ≥ 6 mg/dl	47 (81)	134 (42)	< 0.001

N_o: number of patients with available data for each characteristic; n: number of patients with attribute out of N_o; %: percent of n out of N_o; ULT: urate-lowering therapies; SU: serum urate.

interest was evaluated in a univariable model and those factors with a resulting p value < 0.20 were further evaluated in the multivariable logistic models (Table 5). Although sex and age at enrollment were not significant at the 20% α level in univariable models, they were included in the final multivariable models.

Those factors with a resulting p value < 0.20 were further evaluated in a multivariable logistic model. Prior to the multivariable model, we evaluated the possible existence of multicollinearity among the predictor variables in the multivariable model. Variables found to be pairwise correlated at a level > 0.20 or –0.20 were flagged. As expected, the number of flares (because it is the sum of flares resulting in an ER visit, an MD visit, or flares with no medical attention sought) was correlated with its 3 components, and the correlation among the 3 components ranged from 0.24 to 0.40. In addition, the number of flares was also correlated with pain (0.25) and disease activity (0.32), and pain and disease activity were correlated (0.56). Variables that indicate the use of allopurinol and febuxostat were also correlated (–0.65). We therefore created a combined variable for allopurinol and febuxostat use with the following categories: not receiving either drug, allopurinol 50–200 mg, allopurinol > 200–300 mg, allo-

Table 5. Multivariable OR and 95% CI from logistic regression. Sex and age at enrollment are included in model although not significant at the 0.020 level in the univariable models. Values are AOR (95% CI).

Variables	Model with No. Flares in Last Yr	Model with Patient-reported Disease Activity
Sex, female is ref.	1.37 (0.92–2.04)	1.37 (0.93–2.04)
Age at enrollment, yrs, < 65 is ref.	1.19 (0.87–1.63)	1.18 (0.87–1.62)
Marital status, single is ref.		
Married/partnered	1.51 (0.93–2.47)	1.41 (0.87–2.28)
Other	1.74 (0.97–3.11)	1.64 (0.92–2.90)
Yrs of gout, > 1 vs ≤ 1 ref.	1.84 (1.14–2.96)	2.18 (1.37–3.47)
Hospitalization last 3 yrs, yes vs no ref.	1.10 (0.38–3.23)	1.01 (0.34–2.99)
SU at first visit, ≥ 6 vs < 6 ref.	1.48 (1.08–2.04)	1.47 (1.07–2.01)
Urate-lowering drug, mg, dose*		
Allopurinol 50–200	0.62 (0.36–1.04)	0.64 (0.39–1.07)
Allopurinol > 200–300	0.64 (0.39–1.04)	0.65 (0.40–1.05)
Allopurinol > 300	0.77 (0.42–1.42)	0.76 (0.41–1.39)
Febuxostat 40	1.27 (0.66–2.43)	1.28 (0.67–2.43)
Febuxostat 80/other	1.15 (0.59–2.23)	1.08 (0.56–2.09)
Presence of tophi, yes vs no ref.	1.96 (1.36–2.84)	1.91 (1.32–2.75)
No. flares in last yr, > 1 vs ≤ 1 ref.	2.00 (1.46–2.75)	—
Patient-reported disease activity, > 10 vs ≤ 9 ref.	—	1.33 (1.33–2.48)

* Allopurinol or febuxostat (not receiving either drug is ref.). AOR: adjusted OR; ref.: reference.

purinol > 300 mg, febuxostat 40 mg, and febuxostat 80 mg/other. We further fit 2 final models, 1 each for the number of flares and disease activity. Each of the 2 models further included marital status, years of gout, hospitalization in the last 3 years, serum acid level, combined allopurinol and febuxostat use, and presence of tophi because these were significant at the 0.2 level in univariate analyses. Sex and age at enrollment were also included in the final models. To account for the clustering of patients by physician, we evaluated practice site as a random effect in the final multivariable model. Because this effect proved to be significant, the final models shown in Table 4 include adjustment for physician effect.

DISCUSSION

According to the 2012 ACR guidelines[14], antiinflammatory drugs for flare prophylaxis are recommended when ULT are initiated and should be continued if there is continuing gout disease activity and/or the SU target has not been achieved. In our study, we found that only 42% of patients with gout in the CORRONA Gout Registry were receiving gout flare prophylaxis. Because ours was a retrospective study, we may not have identified patients previously receiving prophylaxis. The most common drugs used for prophylaxis among the CORRONA Gout Registry patients were colchicine (78%) and NSAID (32%). Prophylaxis drug combination was used in 45 patients (10.2%). Only 26% (10% colchicine and 16% NSAID) of patients with gout were receiving gout flare prophylaxis in a study of 643 patients receiving a new allopurinol prescription[17]. In a 2002 study of gout treatment patterns in the United States, whereas about 2.8 million prescriptions for allopurinol were issued, only 381,000 prescriptions for colchicine and 700,000 prescriptions for NSAID were issued, which may or may not have been for prophylaxis[18].

To our knowledge, our study is the first to evaluate whether differences in disease characteristics influenced the use of prophylaxis. We found prophylaxis to be significantly more common in patients with higher disease activity. Thus patients with ≥ 1 flare in the year previous to enrollment, greater healthcare use, higher ULT doses, and presence of tophi contributed to increased use of prophylaxis. Patients who reported greater disease activity and pain were also more likely to receive prophylaxis. This was in agreement with the ACR guidelines, which support prophylaxis in patients with continuing disease activity. Interestingly, many patients receiving prophylaxis had a disease duration of ≥ 1 year, and although length of observation was not specified, secondary to our study's retrospective design, we suggest that further studies are needed to assess appropriate length of prophylaxis.

Prophylaxis during ULT initiation can reduce the incidence and severity of gout flares. The efficacy of colchicine prophylaxis has been established, with lower rates of flare recurrence and less-severe flares in patients who received colchicine compared with placebo[5,7,14,17,18]. The guidelines[12] recommend low-dose colchicine (0.5 mg or 0.6 mg orally) once or twice daily. Prophylactic doses of colchicine are generally well tolerated[5,7]; however, for patients with severe CKD (creatinine clearance < 30 ml/min), the recommended colchicine dose is 0.3 mg/day and was given to 2 of the 4 patients receiving colchicine prophylaxis in our cohort[19]. We found patients to be commonly treated with NSAID prophylaxis despite having CKD. Although current treatment recommendations suggest NSAID as an option for gout prophylaxis, the longterm safety of NSAID may be an issue[20] and contributes to them not being an appropriate choice for gout flare prophylaxis, although no guidelines for safe dosing have been established in the CKD population.

IL-1 inhibitors may be a useful alternative for patients who are intolerant to or have contraindications for colchicine or NSAID. The proinflammatory cytokine IL-1 is involved in mediating the inflammation in gout[13,21]. In our study, anakinra, an IL-1 receptor antagonist, was used for prophylaxis in less than 1% of patients. In clinical trials, rilonacept and canakinumab, IL-1 inhibitors, demonstrated significant flare prevention during ULT initiation[22,23].

There are a number of strengths and potential limitations in our study. Our analysis represents a large US-based observational study of gout treatment. Moreover, the data collection covered 34 practices and more than 80 rheumatol-

ogists, with the majority of the data collected from community-based rheumatology practices. This approach is consistent with the recommendations from the National Institutes of Health Roadmap Initiative to reengineer the clinical research enterprise, including community-based investigators who can expedite study recruitment. In addition, we were able to examine both physician-derived and patient-derived outcome measures, and account for a broad set of potential confounding variables. Nevertheless, the generalizability of our study results remains a potential limitation of our study[10]. It is possible that potential explanatory factors that were not part of the study data collection could influence the study results, such as medication adherence and patient literacy.

Effective ULT treatment and SU reduction can be achieved with old ULT as well as with newer ULT and those in development[4,18]. However, initiation of these therapies is also associated with a high incidence of flares. Therefore, it is increasingly important that prophylaxis be an integral part of chronic gout treatment. Our study highlights disease characteristics influencing the use of prophylaxis and advances our knowledge on the current use of gout flare prophylaxis. Despite the 2012 ACR guidelines for use of antiinflammatory drugs for flare prophylaxis[14], antiinflammatory prophylaxis is not commonly prescribed.

Gout flare prophylaxis needs to be an integral part of chronic gout treatment. However, gout prophylaxis is used uncommonly. Our study highlights disease characteristics influencing the use of prophylaxis and furthers our knowledge on the current use of gout flare prophylaxis.

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