



Pharmacist-managed titration of urate-lowering therapy to streamline gout management

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Received: 13 April 2019 / Accepted: 23 May 2019 / Published online: 30 May 2019
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Abstract

The treat-to-target approach for serum uric acid is the recommended model in gout management according to the 2012 American College of Rheumatology (ACR) guidelines. Adherence to urate-lowering therapy (ULT) can be difficult for patients due to barriers, which include medication burden, financial hardship, and lack of medical literacy. Our aim was to create a pharmacist-managed referral for the titration of ULT to target serum uric acid (sUA) levels in a complex patient population. We utilized a clinical database to query patients seen at a rheumatology clinic over a 12-month period with an ICD-10 diagnosis for gout. The referral criteria were indications for ULT per the 2012 ACR guidelines. Rheumatology providers, consisting of attendings, fellows, and a physician assistant, were asked to refer the identified patients to the pharmacist-managed titration program. The intervention group consisted of 19 referred patients and the control group consisted of 28 non-referred patients. The baseline sUA (median (IQR)) at the time of referral was 8.8 (2) mg/dL for the intervention group and 7.6 (2.8) mg/dL for the control group ($p=0.2$). At the end of the study period, the sUA was 6.1 (1.4) mg/dL for the intervention group and 6.8 (3.2) mg/dL for the control group ($p=0.08$). At the end of the study period, 6 of 19 (32%) intervention group and 7 of 28 (25%) control group were at goal ($p=0.3$). A newly instituted pharmacist-managed titration program was able to achieve lower average sUA levels in referred patients compared to demographically similar individuals who received standard gout management.

Keywords Crystal arthropathies · Hyperuricemia · Gout · Patient compliance

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Key points

1. Recognize barriers to adherence of urate-lowering therapy by patients and providers.
2. A pharmacist-managed program can be effective at improving gout management in a complex patient population.

Introduction

Gout is an inflammatory crystalline arthritis characterized by episodes of painful joint attacks related to monosodium urate (MSU) deposition from excessive serum uric acid (sUA). It is the most common inflammatory arthritis in older individuals, estimated to affect 8.3 million people (3.9% of adults) in the United States [1]. Individuals with gout have more comorbidities compared to the general population, including hypertension, chronic kidney disease (CKD), obesity, diabetes, coronary artery disease, and stroke, and the prevalence of these conditions increases with the level of hyperuricemia [2]. A longer duration of gout is also associated with an increased risk of death from both cardiovascular and non-cardiovascular causes [3]. Furthermore, gout severity is associated with greater healthcare utilization including subspecialty, primary care, and emergency department visits [4]. It is imperative to achieve adequate control of the disease process to improve patient outcomes.

The challenges in the management of gout are multifactorial, including factors related to patients, the healthcare system, socioeconomic, therapies, and comorbidities [5]. Of these barriers, medication non-adherence remains the biggest challenge on both a patient and provider level [6–9]. The 2012 American College of Rheumatology (ACR) and 2016 European League Against Rheumatism (EULAR) guidelines recommend a treat-to-target approach for sUA to prevent gout flares, with a target of sUA < 6.0 mg/dL or sUA < 5.0 mg/dL in the presence of tophaceous or erosive disease [10].

Harborview Medical Center (HMC) is a 413-bed county hospital in Seattle, Washington, which has over 247,000 outpatient clinic visits per year. The rheumatology clinic at HMC serves a complex patient population including indigent and immigrant patients. The goal of this study is to improve gout management of a complex patient population seen at a Seattle county hospital by establishing a pharmacist-managed titration program of ULT titration using the treat-to-target approach.

Methods

Potential patients for referral were identified by querying a clinical database for patients seen at the HMC rheumatology clinic over a 12-month period who had an ICD-10 diagnosis for gout. The referral criteria were indications for ULT per the 2012 ACR guidelines; that is, if the most recent sUA level was > 6 mg/dL or > 5 mg/dL in the presence of tophaceous or erosive disease. Rheumatology providers, consisting of attendings, fellows, and a physician assistant, were asked to consider referral of patients to the clinical pharmacists for assistance with the titration of ULT, as well as other aspects of appropriate gout management such as flares, lab monitoring and prophylactic medications.

The clinical pharmacists used a gout management protocol derived from the available guidelines. Allopurinol was the first-line ULT agent and febuxostat was the second-line agent. Prior to initiating therapy, pharmacists ensured that HLA-B*5801 status was checked for patients of Han Chinese, Thai, or Korean (with stage 3 CKD or greater) descent. The starting dose for allopurinol was 100 mg daily for patients with estimated glomerular filtration rate (eGFR) > 30 mL/min or if eGFR < 30 mL/min, 50 mg daily. The pharmacists ordered repeat sUA levels and complete metabolic panels every 2–5 weeks and increased the ULT dosage as needed, by increments of 50 to 100 mg depending on renal function, until the target sUA was reached and the patient was without flares for 6 months. The maximum allopurinol dose was 900 mg per day. A similar method of uptitration was used for febuxostat when allopurinol was contraindicated, with a maximum dose of 80 mg per day.

In the referral menu, providers were able to choose between several options for flare prophylaxis while ULT was titrated: colchicine 0.6 mg daily, naproxen 250 mg BID with proton pump inhibitor for gastroprotection, or prednisone if the former two were contraindicated (with the dosage recommended per the rheumatology provider). The duration of prophylaxis was either a minimum of 6 months after achieving target sUA or 6 months following the last flare.

The instructions for acute flare were to continue allopurinol and to add an acute flare medication. The options were colchicine 1.2 mg followed by 0.6 mg 1 h later and daily, prednisone 30 mg daily (or an alternative provider-preferred taper), naproxen 750 mg then 250 mg every 8 h for 5–7 days until flare resolution, indomethacin 50 mg thrice daily for 5–7 days until flare resolution, sulindac 200 mg twice daily for 5–7 days until flare solution, or anakinra 100 mg subcutaneous daily for 3 days or any provider preferred regimen based on comorbidities and patient preferences.

The pharmacists provided lifestyle and dietary counseling to the patients such as weight loss and increase in physical

activity. They also provided drug–drug interactions monitoring by flagging other providers of high-risk interactions with colchicine and medications that could worsen hyperuricemia such as thiazides and loop diuretics.

Data were reviewed 12 months after the initiation of the referral process. The intervention group consisted of patients who were referred by their rheumatology providers from November 2017 to October 2018. The control group consisted of patients who met the inclusion criteria and were seen at least once for gout from November 2017 to October 2018 but were not referred to the program by their rheumatologist. This latter group of patients represented standard gout management by the rheumatology providers.

The data gathered from chart review included the demographics, date of referral if in the intervention group, baseline sUA, current sUA, and current ULT dose. For the intervention group, the baseline sUA was the most recent sUA checked on or before the date of referral. For the control group, the baseline sUA was either the most recent sUA prior to the first day of the study period or the very first sUA if the patient established care after the study had already initiated.

Descriptive statistics were performed for baseline demographics, using Fisher’s exact test for categorical variables and Wilcoxon tests for continuous variables. Wilcoxon signed rank tests were used to assess for differences between baseline and current sUA levels within groups, while Wilcoxon rank sum tests were used to assess for between-group differences in baseline and current sUA levels, as well as changes in sUA levels from baseline, using a significance level of 0.05. Statistical analysis was conducted using R, version 3.5.1 [11]. Board ethics approval was not required

by the University of Washington Institutional Review Board due to the project designation as quality improvement.

Results

Baseline demographics are shown in Table 1. The intervention group consisted of 19 patients with a median (IQR) age of 61 (18) years. Of these 19 patients, 13 were male,

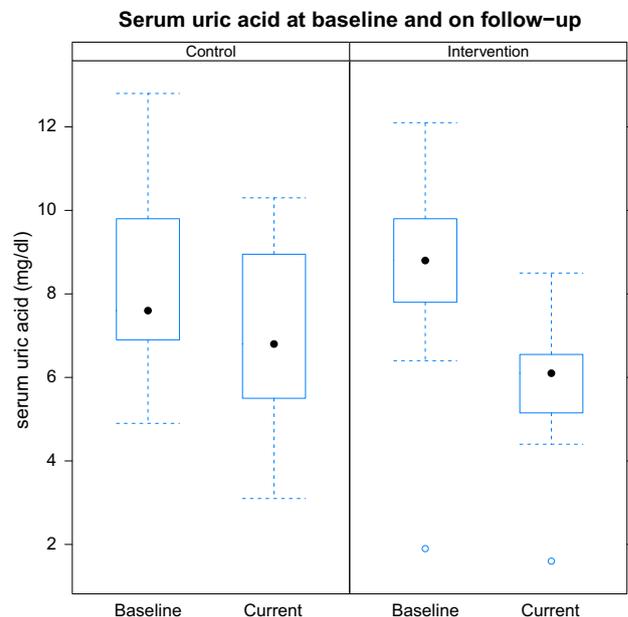


Fig. 1 Comparison of serum uric acid levels in the intervention and standard treatment groups, at baseline and at follow up

Table 1 Baseline demographics of the intervention and standard treatment groups

	Intervention (n = 19)	Control (n = 28)	p value ^a
Median age (IQR), years	61 (18)	54 (14)	0.07
Male gender	13 (68%)	23 (82%)	0.6
Race/ethnicity			0.3 ^b
Caucasian	5 (26.3%)	9 (32.1%)	
Asian	6 (31.5%)	5 (17.9%)	
Pacific Islander	1 (5.3%)	3 (10.7%)	
African American	5 (26.3%)	8 (28.6%)	
Hispanic	1 (5.3%)	0 (0.0%)	
Unknown	1 (5.3%)	3 (10.7%)	
Primary language			1.0
English	12 (63%)	27 (96%)	
Non-english	7 (37%)	1 (4%)	
Tophaceous/erosive disease	9 (47%)	15 (54%)	0.8
Chronic kidney disease	6 (32%)	11 (39%)	0.76

^ap values were calculated using Fisher’s exact test for categorical variables and Wilcoxon tests for continuous variables

^bFor the comparison of white versus non-white race

12 reported English as their primary or preferred language, and 9 had tophaceous or erosive disease. The control group consisted of 28 patients with a median (IQR) age of 54 (14) years; of these 23 were male, 27 reported English as their primary or preferred language, and 15 had tophaceous or erosive disease.

At the end of the follow-up period, the average doses of allopurinol were 388.5 mg and 279.2 mg, and the average doses for febuxostat were 76 mg and 40 mg, for the intervention and control groups, respectively ($p=0.07$ for allopurinol and $p=0.04$ for febuxostat). The intervention group had a total of 50 clinic visits, consisting of both rheumatology provider and clinical pharmacist encounters. The control group had a total of 57 visits with their rheumatology providers.

Changes in the sUA over the course of the intervention period are shown for both groups in Fig. 1. The median (IQR) baseline sUA at the time of referral was 8.8 (2) mg/dL for the intervention group and 7.6 (2.8) mg/dL for the control group ($p=0.2$). At the end of the study period, the median (IQR) sUA was 6.1 (1.4) mg/dL for the intervention group and 6.8 (3.2) mg/dL for the control group ($p=0.08$). At the end of the study period, 6 of 19 (31%) intervention group and 7 of 28 (25%) control group were at goal ($p=0.3$).

Discussion

The goal of this project was to improve gout management in a complex patient population seen at HMC by establishing a pharmacist-managed titration program. In our study, the pharmacist-managed program improved gout management by achieving lower sUA levels than the standard approach by rheumatology providers alone. The intervention group also had more patients at goal, although this comparison did not reach statistical significance.

Gout is the most common inflammatory arthritis in older individuals affecting over 8.3 million people in the United States [1]. Despite individuals with gout having more comorbidities and higher mortality, the burden of poor medication adherence in gout is high [5–9]. Some of the factors contributing to poor patient adherence include language barriers, socioeconomic difficulties, and poor medical literacy.

There have been multiple prior efforts to develop innovative ways to improve gout management in the outpatient setting [12–15]. In a recent randomized controlled trial (RCT), nurse-led care was efficacious and cost-effective with respect to gout outcomes in comparison to usual care [12]. The study highlighted the importance of appropriate education and patient engagement. Furthermore, it supported the importance of the treat-to-target approach for ULT titration to improve patient outcomes.

The pharmacist-staffed RCT by Goldfien et al. achieved 35% of patients at goal by the end of the study [14]. Their

telephone-based program focusing on ULT titration was able to reduce the mean sUA by 1.5 mg/dL after 26 weeks. While we did not randomize our patients to our intervention, we did note similar success with 31% of our intervention group at goal with a sUA decrease of 2.7 mg/dL after 12 months.

A similar pharmacist-led project by Michaud et al. resulted in 73% of their intervention group achieving sUA < 6 mg/dL, with an average time of 10 weeks to reach the treat-to-target goal [15]. The average ULT doses at the end of the study were 296 mg/day for allopurinol and 80 mg/day for febuxostat. One notable difference compared to our project was the patient population. The complex patients in our project required more time to reach the sUA goals. We had a higher mean allopurinol dose of 388.5 mg/day compared to 296 mg/day in Michaud et al. study. The mean doses for febuxostat were similar at 76 mg/day and 80 mg/day. The higher ULT dosage requirement is likely related to the higher proportion of more severe gout in our study.

The strength of this project was to create and demonstrate the utility of a multi-disciplinary approach on a complex patient population, which has not been previously established. Even though significant language barriers exist within our intervention group, measures can be taken to overcome this challenge. The success of our program can be attributed to our comprehensive step-by-step protocol and our pharmacists' enthusiasm in educating and motivating our patients. We suspect other factors to also include more timely uptitration of ULT, more personalized education regarding gout and importance of medication adherence and closer monitoring of side effects including flares.

The major limitations of this study are its non-randomized design and small sample size. The intervention group was limited to 19 patients because the referral was restricted to rheumatology providers at one clinic and was not open to referrals from primary care or other speciality clinics. Gout is a condition that can typically be managed in the primary care setting, unless in complex situations such as medication resistance or significant co-morbidities. At this institution, a small proportion of patients with gout are referred to rheumatology for gout management in general. The diverse demographics of both groups in our study were representative of the communities served by HMC. Interestingly, only 63% of the patients in the intervention group spoke English as their primary language, compared to over 96% in the control group. While selection bias during the referral process could be suspected, in which non-English speakers were being preferentially referred to the clinical pharmacists, we believe that this baseline imbalance of patient-level characteristics was more likely due to chance. Individual providers at this clinic chose to refer patients on the basis of their clinic availability.

While we did see a significantly larger change in sUA levels at the end of follow-up in the intervention group, we believe the challenges of caring for immigrant and indigent patients remain. They required more effort, resources, and time to achieve target sUA. However, this, in turn, can result in fewer patients getting to their sUA goal, especially in the setting of a large number of patients with tophaceous disease. Innovative care methods must be established to overcome these challenges.

Conclusion

At our institution, a newly instituted pharmacist-managed titration program was able to achieve lower average sUA compared to demographically similar individuals in the control group who received standard gout management. Pharmacists should be integrated into the rheumatology clinic to help patients reach their sUA goals.

Author contributions Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work: IJH, JWJ, MBM, SZ, CC, AMB. Drafting the work or revising it critically for important intellectual content: IJH, JWJ, MBM, SZ, CC, AMB. Final approval of the version to be published: IJH, JWJ, MBM, SZ, CC, AMB. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: IJH, JWJ, MBM, SZ, CC, AMB.

Funding Jean W. Liew is supported by a National Institutes of Health training Grant (T32AR007108).

Compliance with ethical standards

Conflict of interest The authors declare they have no conflicts of interest.

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