Effectiveness of a pharmacist-based gout care management program in a large integrated health plan: Results from a pilot study

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Effectiveness of a pharmacist-based gout care management program in a large integrated health plan: Results from a pilot study

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Article Summary

1. Article focus: Hypotheses addressed

- A structured, goal-directed program is effective in achieving optimal control of serum uric acid levels in patients with recurrent gout.
- Successful management of recurrent gout can employ a leveraged approach using a pharmacist-staffed protocol with supervision by a rheumatologist.
- Chronic gout can be managed efficiently, safely and cost-effectively using a telephone-based 'virtual clinic'.

2. Key messages

- A protocol based, goal directed gout management program is highly effective in achieving and maintaining serum uric acid control in patients with recurrent gout.
- Effective urate lowering therapy can be achieved in a high percentage of gout patients using approved doses of allopurinol when dose titration is used.
- This program appears to be a promising approach to improving gout management and may offer significant efficiency compared to current practice.

3. Strengths and Limitations

Strengths: The population we studied is representative of gout patients seen in general rheumatology practice, and therefore our results should be widely generalizable. Our program is relatively easy to implement and requires only a trained clinical pharmacist and rheumatologist to carry out.

Limitations: Although encouraging, this pilot study does not prove that our gout management program is more effective than usual care for gout because there was no control group. A study testing this hypothesis is needed. The structure of our organization, which integrates the health plan, pharmacy programs and physician care, is optimal for the use of our program. A non-integrated system might lead to barriers in setting up a similar collaboration. This may limit the applicability of the model.

Abstract

Background:

The incidence of gout has been steadily rising. While effective treatments are available, treatment is often unsuccessful because current approaches to management lack a systematic approach. To address this shortcoming we tested a protocol-based, pharmacist-staffed intervention to manage patients with recurrent gout.

Methods:

Patients in Kaiser Permanente, Northern California (KPNC) with recurrent gout were referred by their primary care physicians to a pharmacist-staffed gout management clinic supervised by a board-certified rheumatologist. The pharmacist used a protocol that employs standard gout medications to achieve and maintain a serum uric acid (sUA) level of 6.0 mg/dl or less. Results from the first 100 consecutive patients enrolled in this pilot program are reported here.

Results:

In 95 evaluable patients enrolled in our pilot program, a sUA of 6.0 mg/dl or less was achieved and maintained in 78 patients with 4 still in the program to date. Five patients declined to participate after referral, and another 13 patients did not complete the program.

Conclusions:

A structured pharmacist-staffed program can effectively and safely lower and maintain uric acid levels in a high percentage of patients with recurrent gout. This care model is simple to implement, efficient and warrants further validation in a clinical trial.

Introduction

Gout is the most common inflammatory arthritis in men (1) and results in considerable morbidity and utilization of health care resources. (2) The past 30 years have witnessed a steady increase in the prevalence of gout. (3–5) The causes of this rise in gout prevalence appear to be linked to the increasing prevalence of obesity, diabetes, chronic renal disease and hypertension. (6,7) Unlike other common rheumatic diseases, the underlying cause of gout, chronic elevation of serum uric acid (sUA), is well understood.

Current approaches for management of other common chronic conditions, such as diabetes, are based on the principle that chronic illnesses are best managed by identifying predictors of optimal outcomes, setting treatment targets, and then monitoring for success in treating to the targets. (8) In the case of gout, an appropriate treatment target has been identified by expert panels sponsored by the European League Against Rheumatism (EULAR) (9) and the American College of Rheumatology (ACR). (10) Both recommend that patients with tophaceous or recurrent gout be treated with urate-lowering therapy (ULT) to a target sUA of < 6.0 mg/dl. Unfortunately, only a minority of gout patients receives appropriate treatment, including doses of ULT sufficient to achieve this target. (11) There are several reasons for this deficiency which have been addressed by other authors. (12,13)

To address the problem of inadequate management of gout, we developed a model for gout management consisting of a 'virtual' clinic comprised of a clinical pharmacist under the supervision of a board-certified rheumatologist. Following a written protocol, the

pharmacist initiates, adjusts and monitors the use of standard gout medications for patients referred by their primary care physicians for recurrent or tophaceous gout. Patients are followed by the clinic until they have 2 consecutive target sUA results at least 3 months apart, and are then discharged back to their usual care. We report here the outcomes of a pilot program by presenting the outcomes of the first 100 patients referred to the program.

Methods

Patient referral

Patients with gout whose primary care physicians practice at KPNC in Richmond, CA were eligible for referral to the gout management program. Referral was at the discretion of the primary care physician (sometimes in consultation with a rheumatologist), based on the intent to use urate-lowering therapy (ULT). The clinical pharmacist then telephoned the referred patients, introduced them to the protocol and, if they agreed to participate, entered them into the program. Patients with end stage renal disease were excluded from the program. The pharmacist, under a protocol approved by the Kaiser Permanente East Bay Pharmacy and Therapeutics Committee, was authorized to order relevant laboratory tests and initiate or change orders for the medications used to manage sUA, and for flare prophylaxis. For treatment of acute flares, medication orders were sometimes provided by the rheumatologist if outside the scope of the pharmacy protocol.

Laboratory assessment and monitoring

Baseline laboratory assessment performed on all referred patients consisted of a sUA, alanine aminotransferase (ALT), estimated glomerular filtration rate (eGFR) and complete blood count (CBC). This same panel of laboratory tests was repeated as needed to monitor progress while the patient was enrolled in the gout management clinic.

Treatment protocol

Figure 1 is a schematic diagram of the assessment and treatment protocol. Once entered into the program, baseline laboratory assessment was performed if not available within the prior month. If, at the time of referral, a patient was being treated for an acute flare of gout, this treatment was continued and completed. Once a baseline laboratory assessment was available, ULT was either initiated or adjusted if the sUA was above 6.0 mg/dl. Flare prophylaxis was used in all cases (see below). After any change in ULT, the patient was instructed to return for laboratory assessment (sUA, ALT, CBC, eGFR) in 2 weeks, and report any adverse drug reactions (ADRs) or gout symptoms. ADRs or gout flares were managed by the clinical pharmacist, usually in consultation with the supervising rheumatologist. This process was continued in an iterative fashion until a target sUA of $\leq$ 6.0 mg/dl was achieved. Patients at target were asked to repeat the laboratory assessment in 3 months. At that time, patients still at target were discharged from the clinic and instructed to continue their medications and follow up with their primary care physician. Those not at target were either restarted on their ULT or it was titrated and the level re-tested in 2 weeks. Patients remained in the gout management program until they demonstrated 2 sUAs $\leq$ 6 mg/dl at least 3 months apart.

Pharmacological treatments

ULT was initiated with allopurinol in all patients as first-line therapy unless the patient had a known ADR or allergy to allopurinol. The starting dose for allopurinol-naïve patients was 100 mg daily (some patients were on higher doses at the time of referral). Dose titration for patients not at target sUA was done using 100 mg per day increments, or in some cases, patients on 300 mg daily were titrated to 450 mg daily. Patients already on febuxostat or probenecid were maintained on these and doses titrated as needed based on sUA. Patients who developed a significant ADR or symptoms of allergy to allopurinol were switched to either febuxostat 40 mg daily or probenecid 500 mg daily, depending on their clinical status in consultation with the rheumatologist. Dose titration was then continued with these drugs if needed.

Gout-flare prophylaxis in most instances utilized colchicine 0.6 mg daily. For patients with eGFR less than 30, the dose was reduced to 0.3 mg per day. In some patients, if recommended by the rheumatologist, a daily nonsteroidal anti-inflammatory drug (NSAID) treatment was substituted, if no contraindication prevented this.

Acute gout flares were managed by the clinical pharmacist, in consultation with the rheumatologist, using oral NSAIDS, prednisone or colchicine.

Adverse drug reactions (ADR) to medications, incident gout flares and abnormal laboratory parameters were recorded by the clinical pharmacist at each telephone encounter and reviewed by the rheumatologist for management.

Results

Patient demographics and co morbidities of the pilot sample are described in Table 1.

Table 1. Demographic and clinical characteristics of patients (N=100)

Characteristic

	Mean (range)
Age, years	61 (32-94)
BMI, kg/m^2	31 (20-48)
	Percent
Male	75%
Hypertension	75%
Chronic kidney disease (CKD 2-4)	29%
Diabetes	29%
Coronary artery disease	10%
Congestive heart failure	11%
2 or more co-morbidities	46%

Three-fourths of the patients were male. The mean age was 61 years, (range: 32 – 94 years). The mean body mass index was 31 kg/m^2 (range: 20 – 48 kg/m^2). Common gout-associated co-morbidities were determined based on the presence of specific ICD-9 codes listed in the problem list of each patient in the electronic medical record, and verified by chart review. The majority of patients had at least one of the common co-morbidities associated with gout. Seventy-eight percent had hypertension, 29% had chronic kidney disease (CKD) stage 3 or 4, and 29% had diabetes. A smaller number had either coronary

artery disease or congestive heart failure. Forty-five percent of the patients had 2 or more of these co-morbid conditions.

Figure 2 is a schematic that shows the current status of the first 100 patients referred to our clinic. Five patients declined to participate when initially contacted by the pharmacist. Thus, 95 patients started the program, and at the time of this analysis, 78 had completed the program with 2 consecutive sUA measurements of < 6.0 mg/dl, and 4 were still being managed. Thirteen patients left the program prior to achieving the end point. Of these, 2 patients died while in the program. One died from complications of abdominal surgery and the other, aged 94, died at home of "natural causes". One patient developed symptoms of an allergic reaction to allopurinol and declined further treatment. One patient lost insurance coverage, and another was incarcerated. The remaining 8 patients were discharged by the program pharmacist because of a pattern of non-adherence to treatment or lab monitoring, or because they elected not to complete the program.

Figure 3 shows the sUA's of each patient in the pilot gout-management study as a set of paired samples. Each pair of bars represents the baseline sUA (red bars) and final sUA (blue bars) for each patient. For those patients still in the program (i.e., those who have not yet achieved the discharge criterion of 2 consecutive sUA measurements of $\leq$ 6.0 mg/dl), the blue bar is the most recent sUA available if the patient did not complete the program. The dotted horizontal line represents the sUA target of 6.0 mg/dl. The figure

shows all the patients who entered the program, including those who are still being managed and those who did not complete the program.

To provide a more detailed view of how patients responded to management by the clinic, we plotted sequential sUA levels in a subset of our patients. Figure 4 shows this analysis in 20 randomly selected patients entering the program. Each line represents the sequential sUA measurements of a single patient for a period of 12 months. Essentially all the patients in this random sample initially responded with significant reduction in sUA. In many patients, this improvement was sustained, but in others, the sUA subsequently rose due to discontinuation of ULT. In these patients, the pharmacist was able, in most cases, to restart ULT and continue testing to assure continuing medication adherence. The Figure also shows that by 12 months in the program, 16 of the 20 patients had achieved a target sUA and two had a normal sUA of < 6.8 mg/dl.

Analysis of the 78 patients who have completed the program after achieving and maintaining the targeted sUA showed that 68 (87%, 95% CI: 78% to 94%) were on allopurinol at discharge. Figure 5 shows the distribution of allopurinol doses required to achieve a sUA of $\leq$ 6.0. The mean daily allopurinol dose required to achieve a sUA of $\leq$ 6 was 311 mg. Sixty-eight percent of patients on allopurinol achieved target on 300 mg per day or less. Only three patients achieved goal on the starting dose of 100 mg daily and two patients required 600 mg per day. All five patients on febuxostat had achieved the goal sUA level on 40 mg per day.

Three patients (3%) experienced rash or other symptoms of allergy to allopurinol. None required more than discontinuation of the medication. Of these, two patients were changed to alternative ULT and one patient declined further treatment and discontinued the program. Elevation of ALT was seen at some time during treatment in 47 patients (48%), but only 7 of the patients had elevations high enough to require changing medication. Most stabilized or returned to normal with continued treatment and monitoring. Incident acute gout flares were reported in 33 patients (34%). None resulted in discontinuation of ULT. Gastrointestinal side effects were uncommon and in no case required a change in therapy.

Discussion

Gout is arguably the best understood of the common inflammatory arthritic diseases; effective preventive therapy is readily available and the key outcome (sUA < 6 mg/dl in most cases) is easily measured. Why, then, is unsuccessful control of sUA so frequent? A number of factors contribute to suboptimal gout management. (11,12,14) Adherence to ULT is poor when compared to medication adherence in other chronic conditions. (15) Symptoms are typically intermittent with extended gout-free periods. Moreover, there are effective treatments for gout flares, and medications (for example, colchicine) that can reduce the incidence of flares without lowering sUA. It is not surprising therefore, that many gout patients are never started on, or discontinue ULT. Another important feature of gout management is that initiation of ULT can lead to a short-term increase in incidence of gout flares, (16) further discouraging the continuation of therapy. Better

patient education could be expected to improve long-term medication adherence, but is not consistently provided. (17) While diet is clearly a factor in the development of gout (18), patients and physicians frequently place a disproportionate emphasis on dietary restrictions. (19) Although consensus guidelines recommend treating with ULT to a target sUA of 6.0 mg/dl or less, concerns about allopurinol toxicity may discourage some physicians from achieving this goal. In particular, limiting doses of allopurinol in patients with CKD lead to a high percentage of treatment failures (20). Finally, many clinical laboratories do not correctly identify serum urate concentrations of > 6.8 mg/dl as being abnormal. This leads to under-treatment and considerable confusion about diagnosis and management. (21)

Our pilot program was conceived as a way to re-frame the approach to gout management. We hypothesized that using a structured treat-to-target approach with regular monitoring and a goal-directed intervention would result in a high percentage of patients achieving a target sUA. In particular, the protocol was designed to use a slow titration of ULT along with flare prophylaxis and scheduled follow up calls. We also required sustained control of sUA for at least 3 months as a way to promote longer term medication adherence.

The results of our pilot program suggest that a structured program may be an effective approach to gout management. ULT medications are highly effective, and therefore almost all our patients responded with significant reductions in sUA within weeks of starting the program (Figure 4). Dose titration allowed most patients to achieve a target sUA of $\leq$ 6.0 mg/dl and to-date, all patients have been able to achieve goal using standard

doses of available medications. The demographic and clinical features of the patients in our gout sample were similar to those seen in the general population of gout patients described in previous studies, (22,23) suggesting that our findings should be generalizable to gout populations outside KPNC. A nurse-staffed case management approach has been used and achieved impressive results in controlling sUA in gout patients (24). Our pilot program is also based on a structured management approach, but did not require any clinic visits. This model is highly efficient and therefore suitable for managing a large population of gout patients.

We used a treat-to-target approach and did not limit doses of allopurinol specifically based on renal function. Current recommendations do not support the need to limit allopurinol doses to 100 mg daily in patients with CKD, (25–27) though a low starting dose and slow titration is recommended. (26,28) Indeed, limiting the dose of allopurinol based on the presence of chronic kidney disease has been shown to result in treatment failure in an unacceptably high percentage of patients. (17) Our data confirm this observation: only three of 68 allopurinol-treated patients (4%) completing the program achieved a sUA of $\leq$6.0 on 100 mg daily of allopurinol, and only 68% achieved target with 300 mg daily (Figure 5).

Not surprisingly, we encountered many cases of medication non-adherence. Our protocol, by requiring two consecutive target sUA levels three months apart, was designed with the expectation that adherence to ULT would be inconsistent. We do not know whether our time-limited intervention will ultimately lead to long-term control of sUA in these

patients, but we were able to detect medication non-adherence in the first few months and thus reinforce the importance of long-term ULT. Ideally, monitoring of sUA would continue on a regular basis, as recommended for relevant laboratory parameters in other chronic conditions.

We designed our pilot to be efficient and cost-effective by leveraging physician time. The gout management program, while supervised by a rheumatologist, was staffed by a clinical pharmacist who was carefully trained in the management protocol. The pharmacist was able to manage a cohort of up to about 80 patients at a time while spending only about 6-8 hours per week. The time spent in overseeing and assisting the clinical pharmacist was never more than about 30 minutes per week for the rheumatologist once the program was in place. Moreover, our program did not require any in-person visits. This model suggests a path to improved outcomes in gout patients without generating the magnitude of increased utilization of health care resources that might otherwise be required.

Contributorship Statement

Robert Goldfien

Conceived and developed protocol and program. Participated in collection and analysis of data, and pharmacist supervision. Primary author of manuscript.

Andrew Avins

Consulted on project design, data capture, statistical methods and manuscript editing.

Alice Pressman

Oversaw data analysis and presentation. Consulted on data analysis and manuscript editing.

Alice Hwe

Oversaw development and approval of treatment protocol and supervised clinical pharmacists.

Alice Jacobson

Assisted with data collection and analysis.

Michele Ng and Goldie Yip

Worked directly with subjects to arrange data collection, adjust medications, obtain clinical information and report issues or concerns with supervising rheumatologist

Data sharing
There are no additional unpublished data from this study.

Competing Interests
None

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None

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Figures

Fig. 1 Clinic monitoring and treatment flow diagram

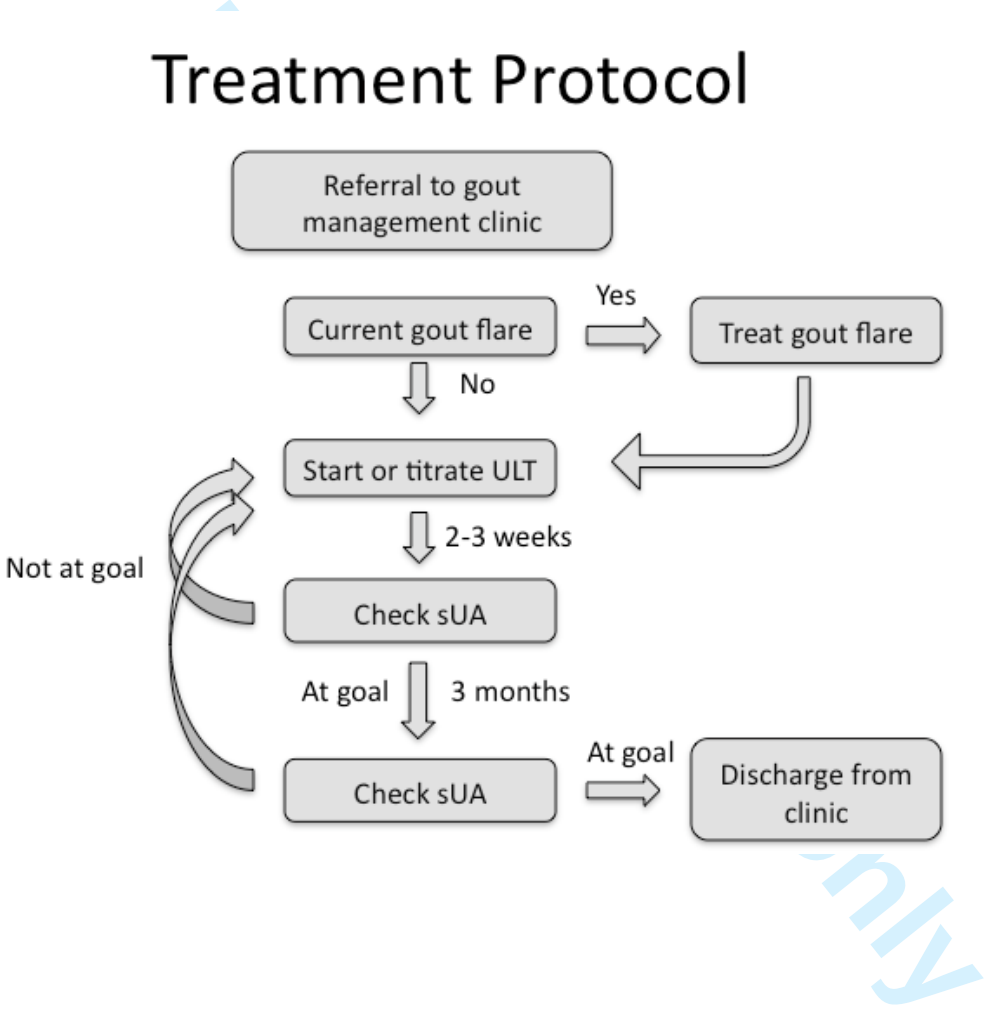


Fig. 2 Current status of first 100 patients referred to program

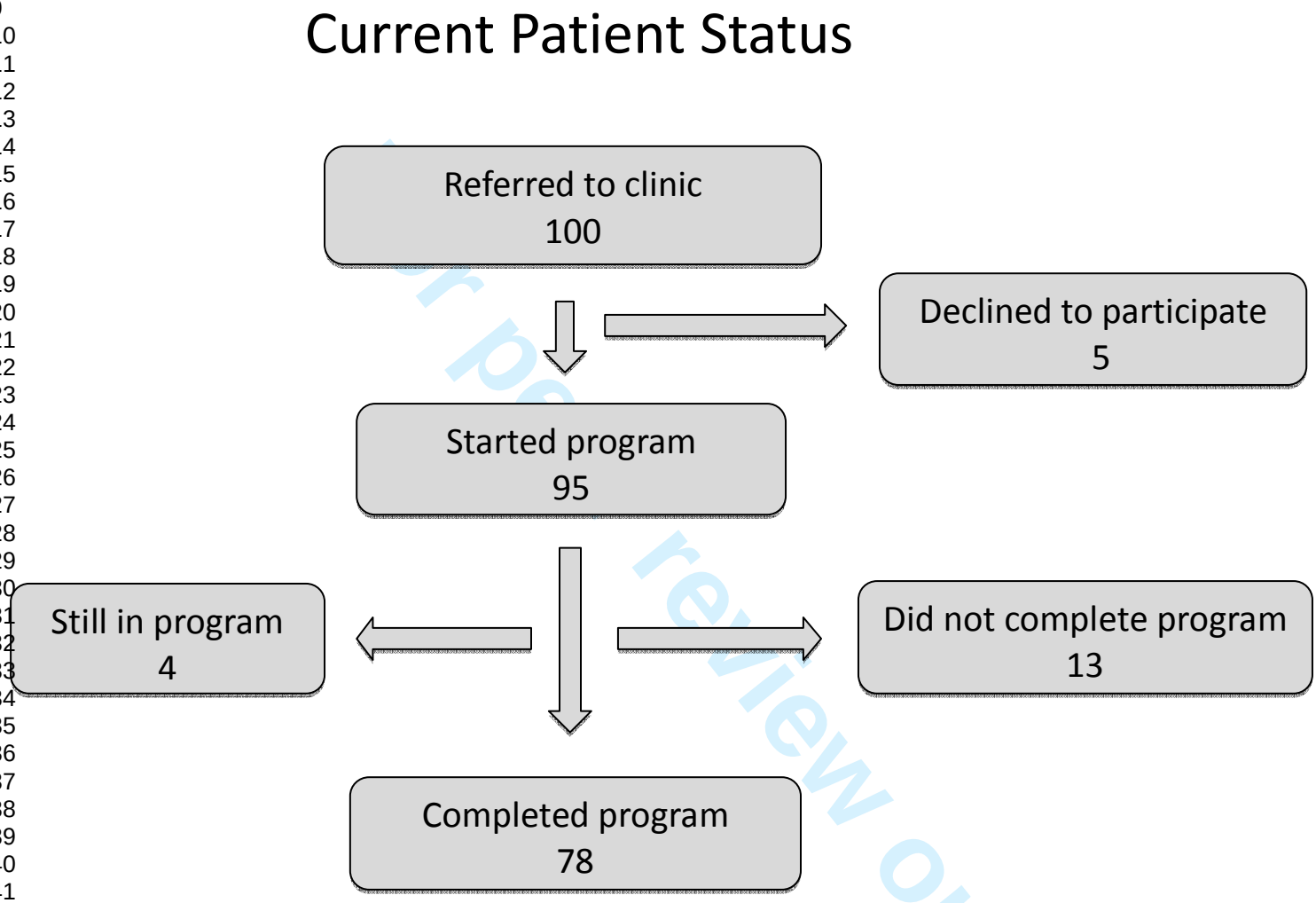


Fig. 3 Comparison of pre-treatment sUA and most recent or final sUA. Each patient is represented by a red bar (initial sUA) and a blue bar (final sUA, whether or not he/she completed the program).

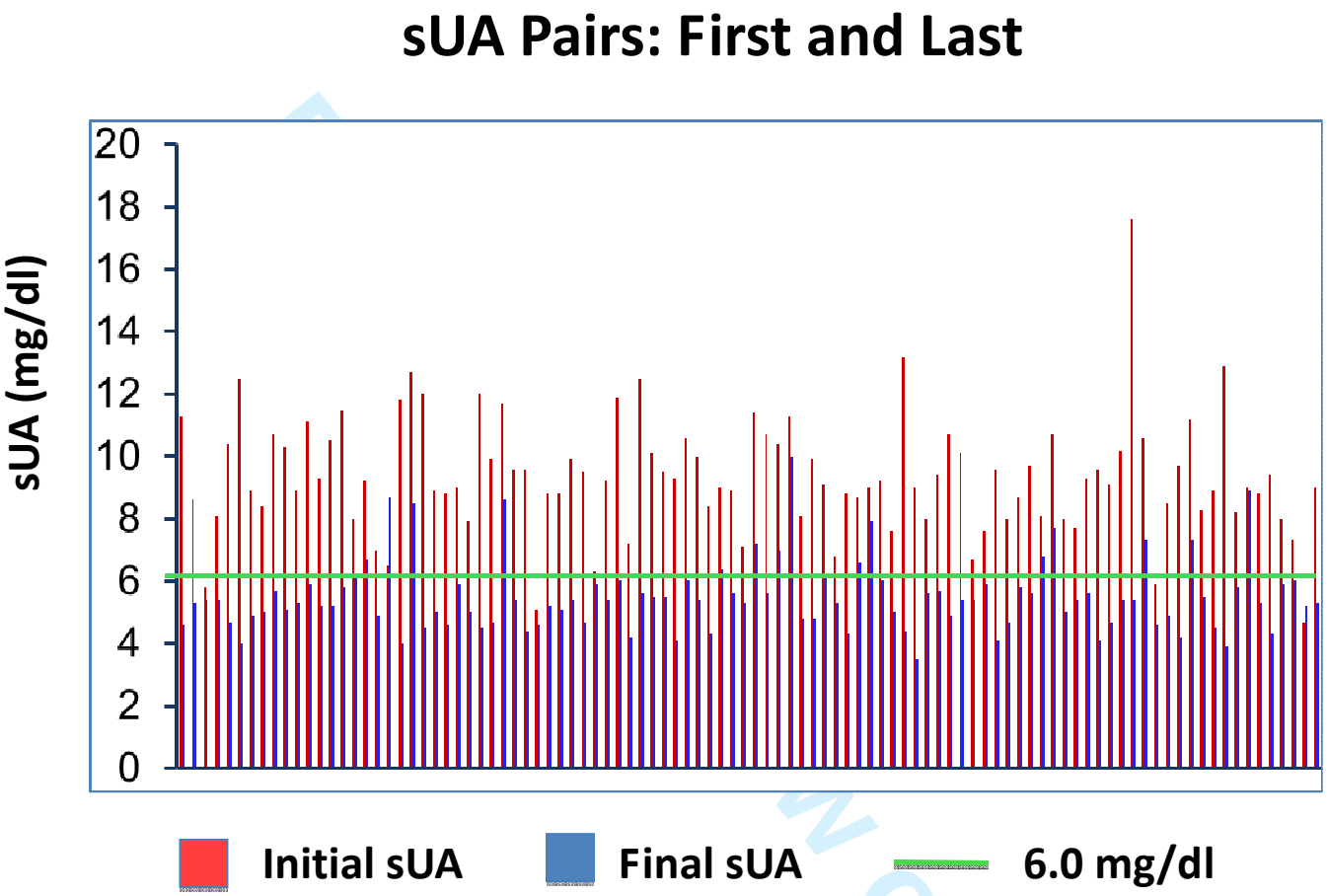


Fig. 4 sUA trend lines for 20 randomly selected patients. Each colored line represents sequential sUA levels in a single patient. Each line stops at the time of clinic discharge or is the most recent sUA if the patient had not completed or left the program.

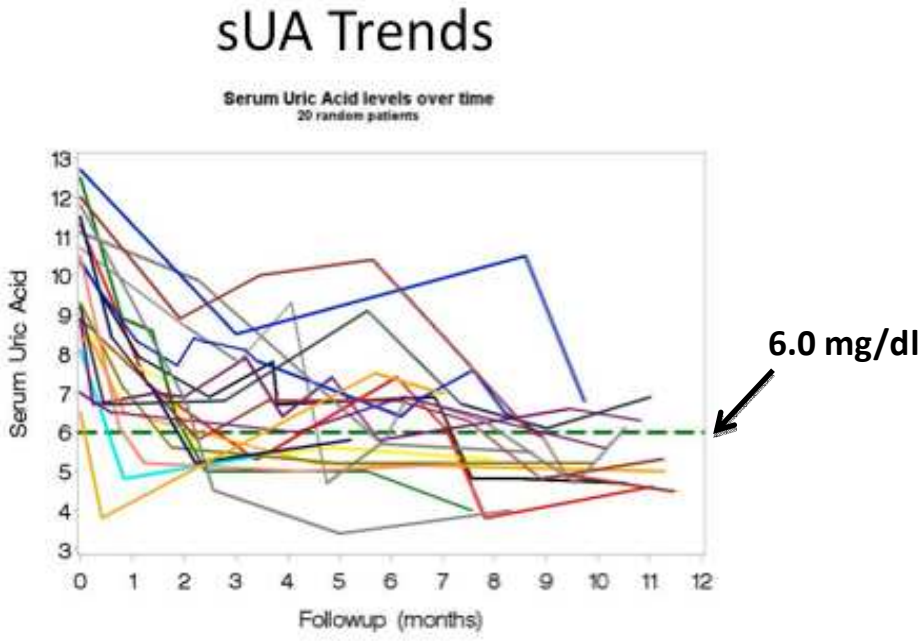
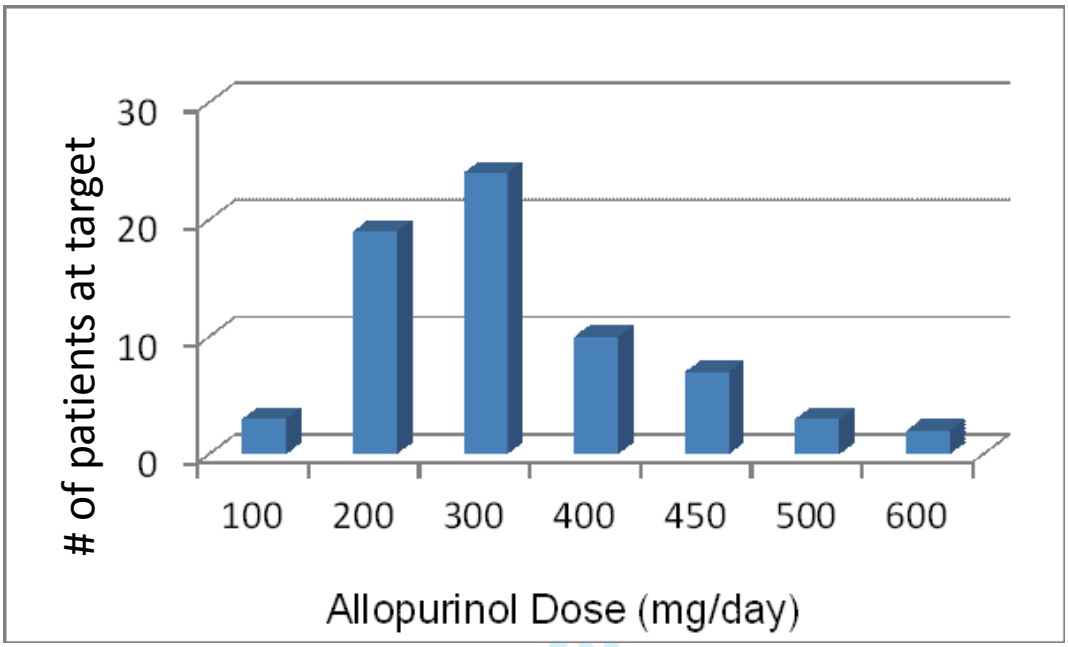


Fig. 5 Dose of Allopurinol required to achieve a sUA of ≤ 6.0 mg/dl



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There is no additional data available

Abstract

Objectives:

The study objective was to determine the feasibility of using a pharmacist-staffed, protocol-based structured approach to improving the management of chronic, recurrent gout.

Setting:

The study was carried out in the outpatient clinic of a single Kaiser Permanente medical center. This is a community based clinic.

Participants:

We report on one hundred consecutive patients between the ages of 21 and 94 (75% male) with chronic or recurrent gout, referred by their primary physicians for the purpose of management of urate lowering therapy. Patients with Stage 5 chronic kidney disease or end-stage kidney disease were excluded.

Interventions:

The program consisted of a trained clinical pharmacist and a rheumatologist. The pharmacist contacted each patient by phone, provided educational and dietary materials, and used a protocol that employs standard gout medications to achieve and maintain a serum uric acid (sUA) level of 6.0 mg/dl or less. Incident gout flares or adverse reactions to medications were managed in consultation with the rheumatologist.

Primary outcome measure:

The primary outcome measure was the achievement and maintenance of a serum uric acid of 6.0 or less for a period of at least 3 months.

Results:

In 95 evaluable patients enrolled in our pilot program, a sUA of 6.0 mg/dl or less was achieved and maintained in 78 patients with 4 still in the program to date. Five patients declined to participate after referral, and another 13 patients did not complete the program. (The majority of these were due to non-adherence.)

Conclusions:

A structured pharmacist-staffed program can effectively and safely lower and maintain uric acid

levels in a high percentage of patients with recurrent gout in a primary care setting. This care model is simple to implement, efficient and warrants further validation in a clinical trial.

Introduction

Gout is the most common inflammatory arthritis in men (1) and results in considerable morbidity and utilization of health care resources. (2) The past 30 years have witnessed a steady increase in the prevalence of gout. (3–5) The causes of this rise in gout prevalence appear to be linked to the increasing prevalence of obesity, diabetes, chronic renal disease and hypertension. (6,7) Unlike other common rheumatic diseases, the underlying cause of gout, chronic elevation of serum uric acid (sUA), is well understood.

Current approaches for management of other common chronic conditions, such as diabetes, are based on the principle that chronic illnesses are best managed by identifying predictors of optimal outcomes, setting treatment targets, and then monitoring for success in treating to the targets. (8) In the case of gout, an appropriate treatment target has been identified by expert panels sponsored by the European League Against Rheumatism (EULAR) (9) and the American College of Rheumatology (ACR). (10) Both recommend that patients with tophaceous or recurrent gout be treated with urate-lowering therapy (ULT) to a target sUA of < 6.0 mg/dl. Unfortunately, only a minority of gout patients receives appropriate treatment, including doses of ULT sufficient to achieve this target. (11) There are several reasons for this deficiency which have been addressed by other

authors. (12,13). The reasons cited have included lack of appropriate monitoring, failure to treat to target and fear of escalation of ULT in some patients, particularly patients with chronic kidney disease. Taken together, it appears that there is a great need for improved approaches to the management of gout.

To address the problem of inadequate management of gout, we developed a model for gout management consisting of a 'virtual' clinic comprised of a clinical pharmacist under the supervision of a board-certified rheumatologist. Following a written protocol, the pharmacist initiates, adjusts and monitors the use of standard gout medications for patients referred by their primary care physicians for recurrent or tophaceous gout. Patients are followed by the clinic until they have 2 consecutive target sUA results at least 3 months apart, and are then discharged back to their usual care. We report here the results of a pilot program by presenting the outcomes of the first 100 patients referred to the program. Though a limited intervention, our intent was to address some of the issues identified in the literature and do it in a way that is highly leveraged and potentially suitable for a large majority of patients with chronic gout who are currently not being adequately managed.

Methods

Patient referral

Patients with gout whose primary care physicians practice at KPNC in Richmond, CA were eligible for referral to the gout management program. Referral was at the discretion

of the primary care physician (sometimes in consultation with a rheumatologist), based on a history of recurrent or tophaceous gout and the intent to use urate-lowering therapy (ULT). Referring physicians were offered the choice of referring each patient for a formal rheumatology consultation, or to the gout management program, supervised by the same rheumatologist (RG). The clinical pharmacist then telephoned the referred patients, introduced them to the protocol and, if they agreed to participate, entered them into the program. Patients consenting to treatment in the program were provided written educational material including dietary guidelines at the time of program entry. Patients with end stage renal disease were excluded from the program. The pharmacist, under a protocol approved by the Kaiser Permanente East Bay Pharmacy and Therapeutics Committee, was authorized to order relevant laboratory tests and initiate or change orders for the medications used to manage sUA, and for flare prophylaxis. For treatment of acute flares, medication orders were sometimes provided by the rheumatologist if outside the scope of the pharmacy protocol.

Laboratory assessment and monitoring

Baseline laboratory assessment performed on all referred patients consisted of a sUA, alanine aminotransferase (ALT), estimated glomerular filtration rate (eGFR) and complete blood count (CBC). This same panel of laboratory tests was repeated as needed to monitor progress while the patient was enrolled in the gout management clinic.

Treatment protocol

Figure 1 is a schematic diagram of the assessment and treatment protocol. Once entered into the program, baseline laboratory assessment was performed if not available within the prior month. If, at the time of referral, a patient was being treated for an acute flare of gout, this treatment was continued and completed. Once a baseline laboratory assessment was available, ULT was either initiated or adjusted if the sUA was above 6.0 mg/dl. Flare prophylaxis was used in all cases (see below). After any change in ULT, the patient was instructed to return for laboratory assessment (sUA, ALT, CBC, eGFR) in 2 weeks, and report any adverse drug reactions (ADRs) or gout symptoms. ADRs or gout flares were managed by the clinical pharmacist, usually in consultation with the supervising rheumatologist. This process was continued in an iterative fashion until a target sUA of $\leq$ 6.0 mg/dl was achieved. Patients at target were asked to repeat the laboratory assessment in 3 months. At that time, patients still at target were discharged from the clinic and instructed to continue their medications and follow up with their primary care physician. Those not at target were either restarted on their ULT or it was titrated and the level re-tested in 2 weeks. Patients remained in the gout management program until they demonstrated 2 sUAs $\leq$ 6 mg/dl at least 3 months apart.

Pharmacological treatments

ULT was initiated with allopurinol in all patients as first-line therapy unless the patient had a known ADR or allergy to allopurinol. The starting dose for allopurinol-naïve patients was 100 mg daily (some patients were on higher doses at the time of referral). Dose titration for patients not at target sUA was done using 100 mg per day increments, or in some cases, although selected patients on 300 mg daily were titrated to 450 mg

daily. The maximum allopurinol dose used in the program was 600 mg per day. Patients already on febuxostat or probenecid were maintained on these and doses titrated as needed based on sUA. Patients who developed a significant ADR or symptoms of allergy to allopurinol were switched to either febuxostat 40 mg daily or probenecid 500 mg daily, depending on their clinical status in consultation with the rheumatologist. Dose titration was then continued with these drugs if needed.

Gout-flare prophylaxis was used in all patients and in most instances we utilized colchicine 0.6 mg daily. For patients with eGFR less than 30, the dose was reduced to 0.3 mg per day. In some patients, if recommended by the rheumatologist, a daily nonsteroidal anti-inflammatory drug (NSAID) treatment was substituted, if no contraindication prevented this.

Acute gout flares were managed by the clinical pharmacist, in consultation with the rheumatologist, using oral NSAIDS, prednisone or colchicine.

Adverse drug reactions (ADR) to medications, incident gout flares and abnormal laboratory parameters were recorded by the clinical pharmacist at each telephone encounter and reviewed by the rheumatologist for management.

Results

Patient demographics and co morbidities of the pilot sample are described in Table 1.

Table 1. Demographic and clinical characteristics of patients (N=100)

Characteristic

	Mean (range)
Age, years	61 (32-94)
BMI, kg/m^2	31 (20-48)
	Percent
Male	75%
Hypertension	75%
Chronic kidney disease (CKD 2-4)	29%
Diabetes	29%
Coronary artery disease	10%
Congestive heart failure	11%
2 or more co-morbidities	46%

Three-fourths of the patients were male. The mean age was 61 years, (range: 32 – 94 years). The mean body mass index was 31 kg/m^2 (range: 20 – 48 kg/m^2). Common gout-associated co-morbidities were determined based on the presence of specific ICD-9 codes listed in the problem list of each patient in the electronic medical record, and verified by chart review. The majority of patients had at least one of the common co-morbidities associated with gout. Seventy-eight percent had hypertension, and 29% had chronic kidney disease (CKD). Of these, 2 had stage 2 CKD, 22 had stage 3 CKD and 3 had stage 4 CKD. Another 29% had diabetes. A smaller number had either coronary artery disease or congestive heart failure. Forty-five percent of the patients had 2 or more of these co-morbid conditions.

Figure 2 is a schematic that shows the current status of the first 100 patients referred to our clinic. Five patients declined to participate when initially contacted by the pharmacist. Thus, 95 patients started the program, and at the time of this analysis, 78 had completed the program with 2 consecutive sUA measurements of < 6.0 mg/dl, and 4 were still being managed. Thirteen patients left the program prior to achieving the end point. Of these, 2 patients died while in the program. One died from complications of abdominal surgery and the other, aged 94, died at home of "natural causes". One patient developed symptoms of an allergic reaction to allopurinol and declined further treatment. One patient lost insurance coverage, and another was incarcerated. The remaining 8 patients were discharged by the program pharmacist because of a pattern of non-adherence to treatment or lab monitoring, or because they elected not to complete the program. The time patients spent under program management varied considerably. The mean duration of participation was 47.8 weeks (range 14.9-109.6 weeks). Although our program was a feasibility study and designed as a short term intervention, when we examined the medical records of the 78 patients who have successfully completed the program, we found that 63 of these had been tested at least one time by their regular physician after clinic discharge (mean follow up time 36 weeks) and that 53 of these (80%) still maintained a sUA of 6.0 or less.

Figure 3 shows the sUA's of each patient in the pilot gout-management study as a set of paired samples. Each pair of bars represents the baseline sUA (red bars) and final sUA (blue bars) for each patient. For those patients still in the program (i.e., those who have not yet achieved the discharge criterion of 2 consecutive sUA measurements of ≤ 6.0

mg/dl), the blue bar is the most recent sUA available if the patient did not complete the program. The dotted horizontal line represents the sUA target of 6.0 mg/dl. The figure shows all the patients who entered the program, including those who are still being managed and those who did not complete the program.

To provide a more detailed view of how patients responded to management by the clinic, we plotted sequential sUA levels in a subset of our patients. Figure 4 shows this analysis in 20 randomly selected patients entering the program. Each line represents the sequential sUA measurements of a single patient for a period of 12 months. Essentially all the patients in this random sample initially responded with significant reduction in sUA. In many patients, this improvement was sustained, but in others, the sUA subsequently rose due to discontinuation of ULT. In these patients, the pharmacist was able, in most cases, to restart ULT and continue testing to assure continuing medication adherence. The Figure also shows that by 12 months in the program, 16 of the 20 patients had achieved a target sUA and two had a normal sUA of < 6.8 mg/dl.

Analysis of the 78 patients who have completed the program after achieving and maintaining the targeted sUA showed that 68 (87%, 95% CI: 78% to 94%) were on allopurinol at discharge. Figure 5 shows the distribution of allopurinol doses required to achieve a sUA of $\leq$ 6.0. The mean daily allopurinol dose required to achieve a sUA of $\leq$ 6 was 311 mg. Sixty-eight percent of patients on allopurinol achieved target on 300 mg per day or less. Only three patients achieved goal on the starting dose of 100 mg daily

and two patients required 600 mg per day. All five patients on febuxostat had achieved the goal sUA level on 40 mg per day.

Three patients (3%) experienced rash or other symptoms of allergy to allopurinol. None required more than discontinuation of the medication. Of these, two patients were changed to alternative ULT and one patient declined further treatment and discontinued the program. Elevation of ALT was seen at some time during treatment in 47 patients (48%), but only 7 of the patients had elevations high enough to require changing medication. Most stabilized or returned to normal with continued treatment and monitoring. Incident acute gout flares were reported in 33 patients (34%). None resulted in discontinuation of ULT. Gastrointestinal side effects were uncommon and in no case required a change in therapy.

Discussion

Gout is arguably the best understood of the common inflammatory arthritic diseases; effective preventive therapy is readily available and the key outcome (sUA < 6 mg/dl in most cases) is easily measured. Why, then, is unsuccessful control of sUA so frequent? A number of factors contribute to suboptimal gout management. (11,12,14) Adherence to ULT is poor when compared to medication adherence in other chronic conditions. (15) Symptoms are typically intermittent with extended gout-free periods. Moreover, there are effective treatments for gout flares, and medications (for example, colchicine) that can reduce the incidence of flares without lowering sUA. It is not surprising therefore, that

many gout patients are never started on, or discontinue ULT. Another important feature of gout management is that initiation of ULT can lead to a short-term increase in incidence of gout flares, (16) further discouraging the continuation of therapy. Better patient education could be expected to improve long-term medication adherence, but is not consistently provided. (17) While diet is clearly a factor in the development of gout (18), patients and physicians frequently place a disproportionate emphasis on dietary restrictions. (19) Although consensus guidelines recommend treating with ULT to a target sUA of 6.0 mg/dl or less, concerns about allopurinol toxicity may discourage some physicians from achieving this goal. In particular, limiting doses of allopurinol in patients with CKD lead to a high percentage of treatment failures (20). Finally, many clinical laboratories do not correctly identify serum urate concentrations of > 6.8 mg/dl as being abnormal. This leads to under-treatment and considerable confusion about diagnosis and management. (21)

Our pilot program was conceived as a way to re-frame the approach to gout management. We hypothesized that using a structured treat-to-target approach with regular monitoring and a goal-directed intervention would result in a high percentage of patients achieving a target sUA. In particular, the protocol was designed to use a slow titration of ULT along with flare prophylaxis and scheduled follow up calls. We also required sustained control of sUA for at least 3 months as a way to promote longer term medication adherence. We realize that maintaining treatment for 3 months does not guarantee long term control of sUA. Nevertheless, of the patients for whom a follow up test was available, 80% were

still at target a mean of 36.8 weeks after clinic discharge. As for any chronic condition, optimal outcomes will require some level of structured monitoring.

The results of our pilot program suggest that a structured program may be an effective approach to gout management. ULT medications are highly effective, and therefore almost all our patients responded with significant reductions in sUA within weeks of starting the program (Figure 4). Dose titration allowed most patients to achieve a target sUA of $\leq$ 6.0 mg/dl and to-date, all patients have been able to achieve goal using standard doses of available medications. The demographic and clinical features of the patients in our gout sample were similar to those seen in the general population of gout patients described in previous studies, (22) suggesting that our findings should be generalizable to gout populations outside KPNC. A nurse-staffed case management approach has been used and achieved impressive results in controlling sUA in gout patients (23). Our pilot program is also based on a structured management approach, but did not require any clinic visits. This model is highly efficient and therefore suitable for managing a large population of gout patients, but not necessarily more effective than a case management approach.

There is ample evidence that therapeutic inertia contributes to inadequate results of ULT (24). Our program was designed specifically to counter this problem by including repeated sUA measurements and specified actions based on the results. In addition, our protocol did not limit doses of allopurinol specifically based on renal function, which has been one of several impediments noted in the literature to successful ULT. Current

recommendations do not support the need to limit allopurinol doses to 100 mg daily in patients with CKD, (25–27) though a low starting dose and slow titration is recommended. (26,28) Indeed, limiting the dose of allopurinol based on the presence of chronic kidney disease has been shown to result in treatment failure in an unacceptably high percentage of patients. (17) Our data confirm this observation: only three of 68 allopurinol-treated patients (4%) completing the program achieved a sUA of $\leq$6.0 on 100 mg daily of allopurinol, and only 68% achieved target with 300 mg daily (Figure 5).

Not surprisingly, we encountered many cases of medication non-adherence. In most cases, this was detected in the course of the routine testing that comprised the protocol. Typically a patient whose sUA was at or near target, had a repeat test that was no longer at target. In some cases, non-adherence was discovered at the time the patient called to pharmacist because of a gout flare. Our protocol, by requiring two consecutive target sUA levels three months apart, was designed with the expectation that adherence to ULT would be inconsistent. As noted previously, we do not know whether our time-limited intervention will ultimately lead to long-term control of sUA in these patients, but we were able to detect medication non-adherence in the first few months and thus reinforce the importance of long-term ULT. Ideally, monitoring of sUA would continue on a regular basis, as recommended for relevant laboratory parameters in other chronic conditions. Despite the fact that all patients were prescribed colchicine or NSAIDs for flare prophylaxis, we encountered a substantial number of gout flares during the program. While some increase in flares may be expected, in our experience, many of the flares in our patients occurred in connection with medication non-adherence. This tendency of

gout patients to discontinue ULT accounted for the wide range of times patients had to stay under management. We provided our patients with written educational material as well, but could not evaluate the effectiveness of this.

We designed our pilot to be efficient and cost-effective by leveraging physician time. The gout management program, while supervised by a rheumatologist, was staffed by a clinical pharmacist who was carefully trained in the management protocol. The pharmacist was able to manage a cohort of up to about 80 patients at a time while spending only about 6-8 hours per week. The time spent in overseeing and assisting the clinical pharmacist was never more than about 30 minutes per week for the rheumatologist once the program was in place. Moreover, our program did not require any in-person visits. This model suggests a path to improved outcomes in gout patients without generating the magnitude of increased utilization of health care resources that might otherwise be required. We recognize that pharmacists may not be available or allowed to manage patients as was done in our protocol. Even so, a trained clinical nurse could be substituted in the pharmacist's role and provide excellent care while leveraging physician time.

Contributorship Statement

Robert Goldfien

Conceived and developed protocol and program. Participated in collection and analysis of data, and pharmacist supervision. Primary author of manuscript.

Andrew Avins

Consulted on project design, data capture, statistical methods and manuscript editing.

Alice Pressman

Oversaw data analysis and presentation. Consulted on data analysis and manuscript editing.

Alice Hwe

Oversaw development and approval of treatment protocol and supervised clinical pharmacists.

Alice Jacobson

Assisted with data collection and analysis.

Michele Ng and Goldie Yip

Worked directly with subjects to arrange data collection, adjust medications, obtain clinical information and report issues or concerns with supervising rheumatologist

Data sharing
There are no additional unpublished data from this study.

Funding
None

Competing Interests
None

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Figures

Fig. 1 Clinic monitoring and treatment flow diagram

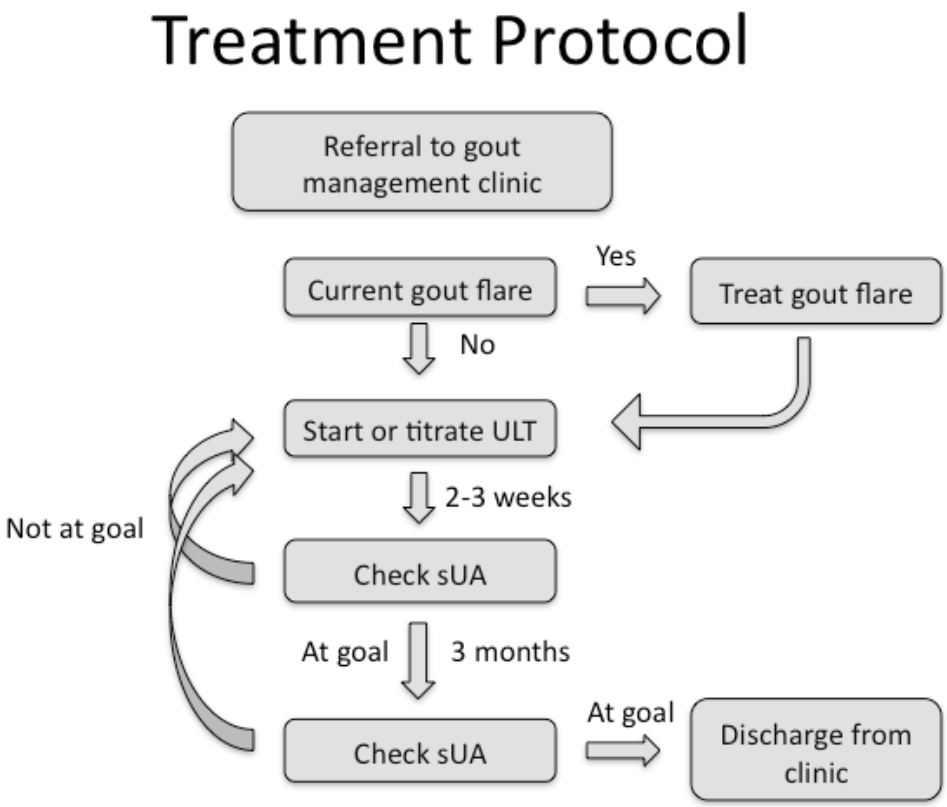


Fig. 2 Current status of first 100 patients referred to program

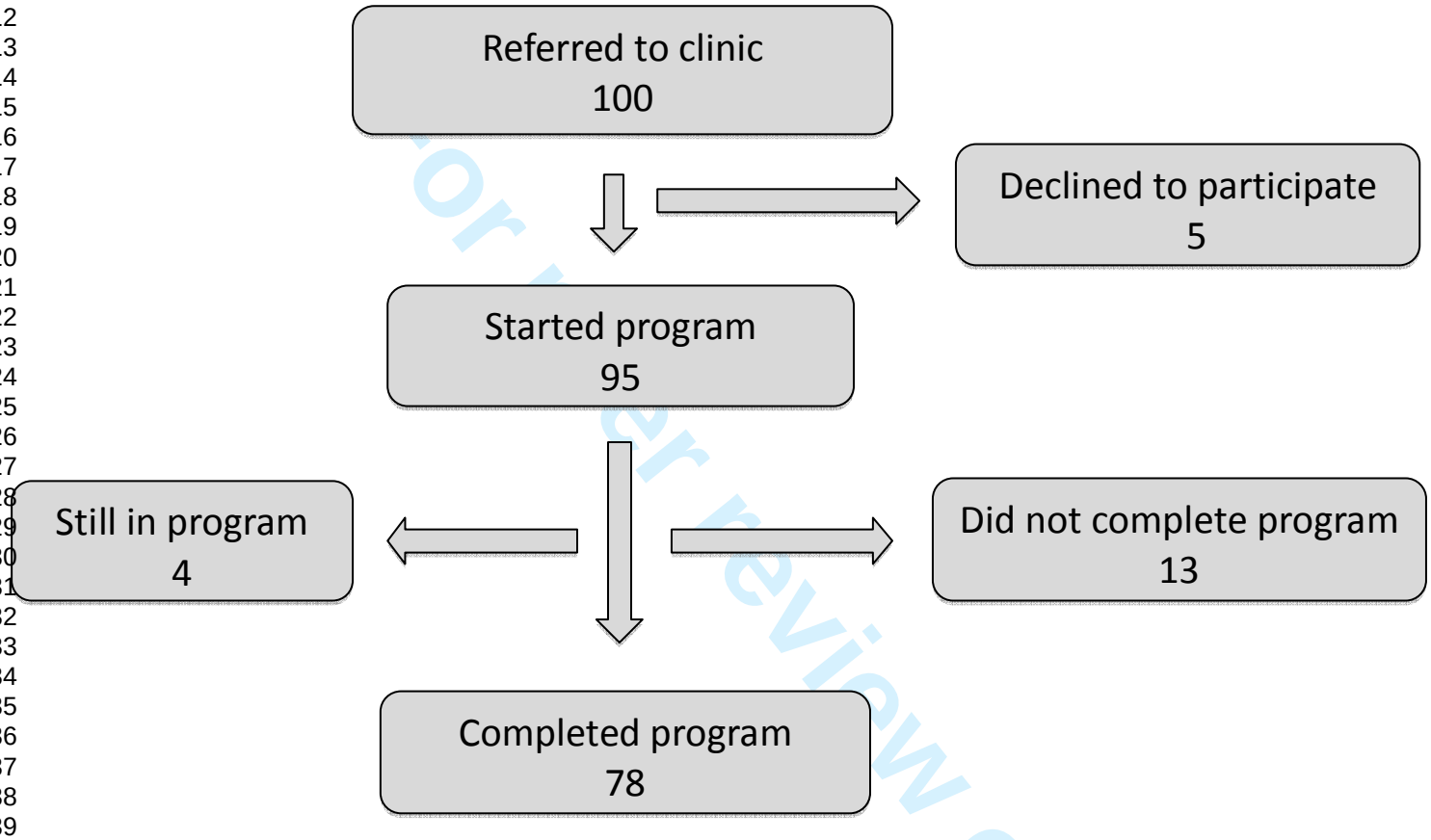


Fig. 3 Comparison of pre-treatment sUA and most recent or final sUA. Each patient is represented by a red bar (initial sUA) and a blue bar (final sUA, whether or not he/she completed the program).

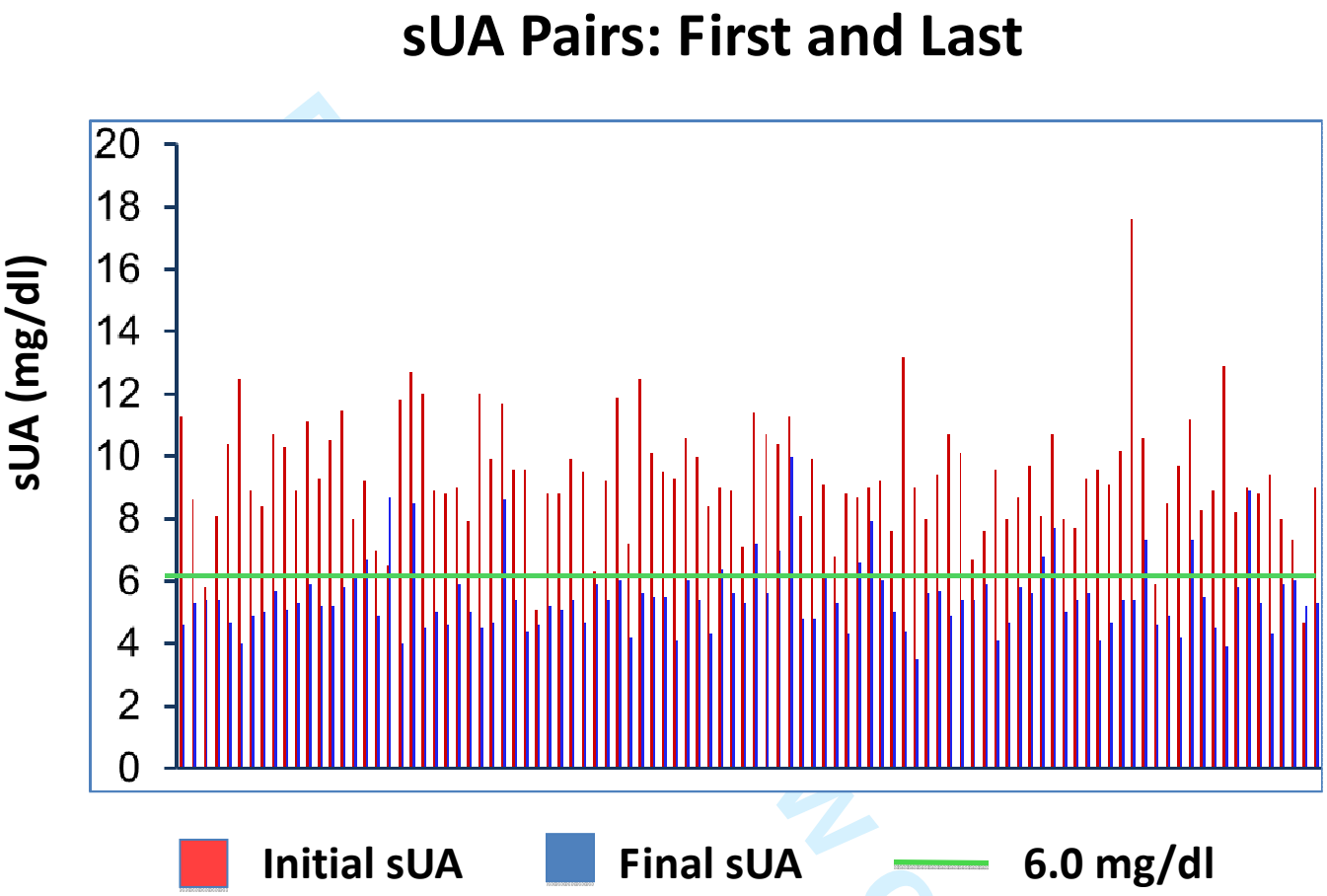


Fig. 4 sUA trend lines for 20 randomly selected patients. Each colored line represents sequential sUA levels in a single patient. Each line stops at the time of clinic discharge or is the most recent sUA if the patient had not completed or left the program.

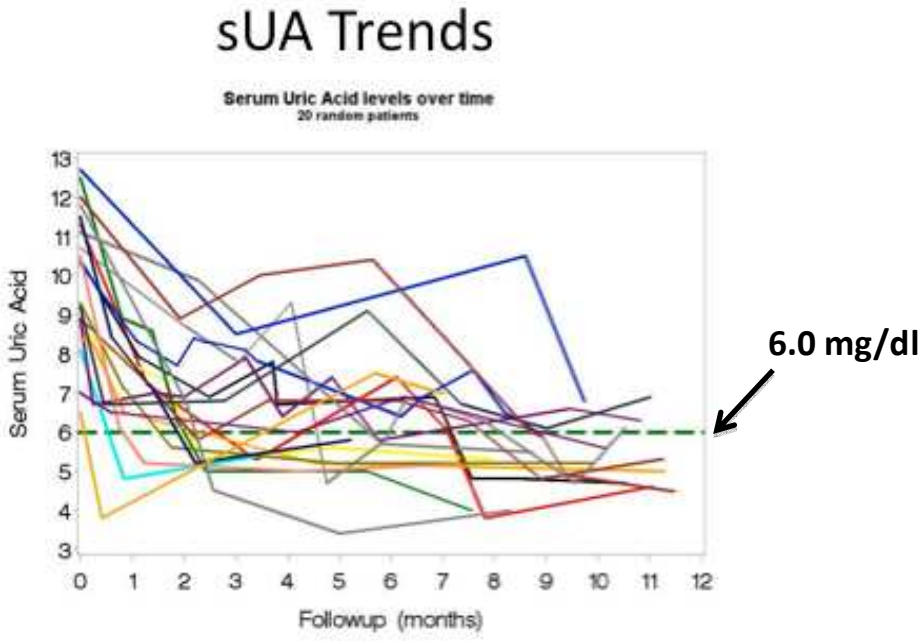
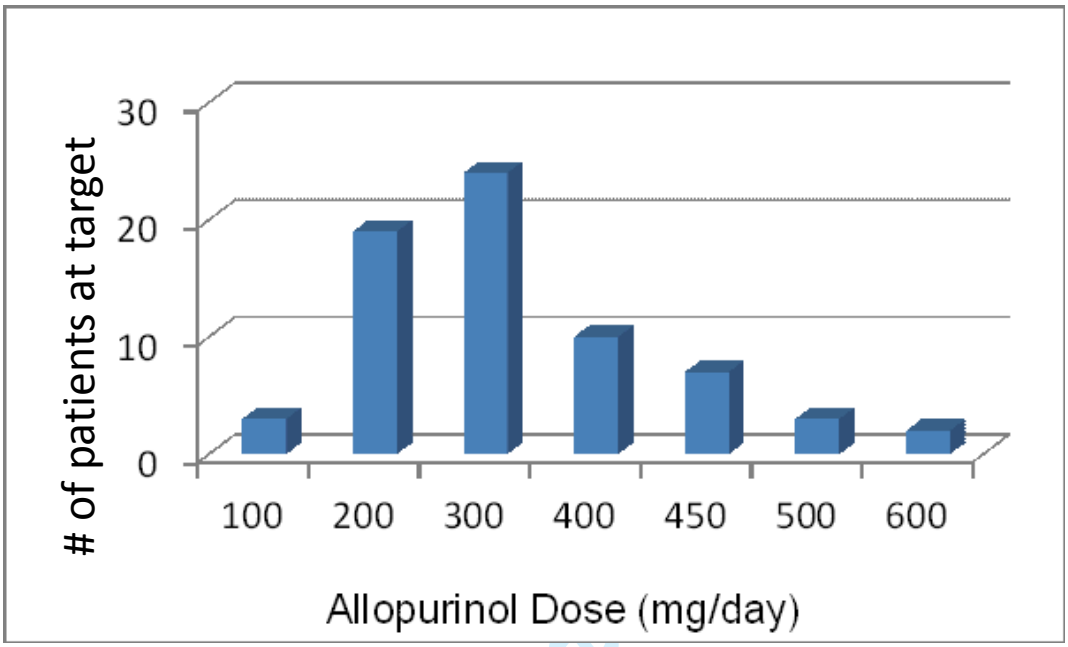


Fig. 5 Dose of Allopurinol required to achieve a sUA of ≤ 6.0 mg/dl



Effectiveness of a pharmacist-based gout care management program in a large integrated health plan: Results from a pilot study

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There is no additional data available

Abstract

Background:

The incidence of gout has been steadily rising. While effective treatments are available, treatment is often unsuccessful because current approaches to management lack a systematic approach. To address this shortcoming we tested a protocol-based, pharmacist-staffed intervention to manage patients with recurrent gout.

Methods:

Patients in Kaiser Permanente, Northern California (KPNC) with recurrent gout were referred by their primary care physicians to a pharmacist-staffed gout management clinic supervised by a board-certified rheumatologist. The pharmacist used a protocol that employs standard gout medications to achieve and maintain a serum uric acid (sUA) level of 6.0 mg/dl or less. Results from the first 100 consecutive patients enrolled in this pilot program are reported here.

Results:

In 95 evaluable patients enrolled in our pilot program, a sUA of 6.0 mg/dl or less was achieved and maintained in 78 patients with 4 still in the program to date. Five patients declined to participate after referral, and another 13 patients did not complete the program. (The majority of these were due to non-adherence.)

Conclusions:

A structured pharmacist-staffed program can effectively and safely lower and maintain uric acid levels in a high percentage of patients with recurrent gout. This care model is simple to implement, efficient and warrants further validation in a clinical trial.

Introduction

Gout is the most common inflammatory arthritis in men (1) and results in considerable morbidity and utilization of health care resources. (2) The past 30 years have witnessed a steady increase in the prevalence of gout. (3–5) The causes of this rise in gout prevalence appear to be linked to the increasing prevalence of obesity, diabetes, chronic renal disease and hypertension. (6,7) Unlike other common rheumatic diseases, the underlying cause of gout, chronic elevation of serum uric acid (sUA), is well understood.

Current approaches for management of other common chronic conditions, such as diabetes, are based on the principle that chronic illnesses are best managed by identifying predictors of optimal outcomes, setting treatment targets, and then monitoring for success in treating to the targets. (8) In the case of gout, an appropriate treatment target has been identified by expert panels sponsored by the European League Against Rheumatism (EULAR) (9) and the American College of Rheumatology (ACR). (10) Both recommend that patients with tophaceous or recurrent gout be treated with urate-lowering therapy (ULT) to a target sUA of < 6.0 mg/dl. Unfortunately, only a minority of gout patients receives appropriate treatment, including doses of ULT sufficient to achieve this target. (11) There are several reasons for this deficiency which have been addressed by other authors. (12,13). The reasons cited have included lack of appropriate monitoring, failure to treat to target and fear of escalation of ULT in some patients, particularly patients with chronic kidney disease. Taken together, it appears that there is a great need for improved approaches to the management of gout.

To address the problem of inadequate management of gout, we developed a model for gout management consisting of a 'virtual' clinic comprised of a clinical pharmacist under the supervision of a board-certified rheumatologist. Following a written protocol, the pharmacist initiates, adjusts and monitors the use of standard gout medications for patients referred by their primary care physicians for recurrent or tophaceous gout. Patients are followed by the clinic until they have 2 consecutive target sUA results at least 3 months apart, and are then discharged back to their usual care. We report here the ~~outcomes~~ results of a pilot program by presenting the outcomes of the first 100 patients referred to the program. Though a limited intervention, our intent was to address some of the issues identified in the literature and do it in a way that is highly leveraged and potentially suitable for a large majority of patients with chronic gout who are currently not being adequately managed.

Methods

Patient referral

Patients with gout whose primary care physicians practice at KPNC in Richmond, CA were eligible for referral to the gout management program. Referral was at the discretion of the primary care physician (sometimes in consultation with a rheumatologist), based on a history of recurrent or tophaceous gout and the intent to use urate-lowering therapy (ULT). Referring physicians were offered the choice of referring each patient for a formal rheumatology consultation, or to the gout management program, supervised by the

same rheumatologist (RG). The clinical pharmacist then telephoned the referred patients, introduced them to the protocol and, if they agreed to participate, entered them into the program. Patients consenting to treatment in the program were provided written educational material including dietary guidelines at the time of program entry. Patients with end stage renal disease were excluded from the program. The pharmacist, under a protocol approved by the Kaiser Permanente East Bay Pharmacy and Therapeutics Committee, was authorized to order relevant laboratory tests and initiate or change orders for the medications used to manage sUA, and for flare prophylaxis. For treatment of acute flares, medication orders were sometimes provided by the rheumatologist if outside the scope of the pharmacy protocol.

Laboratory assessment and monitoring

Baseline laboratory assessment performed on all referred patients consisted of a sUA, alanine aminotransferase (ALT), estimated glomerular filtration rate (eGFR) and complete blood count (CBC). This same panel of laboratory tests was repeated as needed to monitor progress while the patient was enrolled in the gout management clinic.

Treatment protocol

Figure 1 is a schematic diagram of the assessment and treatment protocol. Once entered into the program, baseline laboratory assessment was performed if not available within the prior month. If, at the time of referral, a patient was being treated for an acute flare of gout, this treatment was continued and completed. Once a baseline laboratory assessment was available, ULT was either initiated or adjusted if the sUA was above 6.0 mg/dl. Flare

prophylaxis was used in all cases (see below). After any change in ULT, the patient was instructed to return for laboratory assessment (sUA, ALT, CBC, eGFR) in 2 weeks, and report any adverse drug reactions (ADRs) or gout symptoms. ADRs or gout flares were managed by the clinical pharmacist, usually in consultation with the supervising rheumatologist. This process was continued in an iterative fashion until a target sUA of ≤ 6.0 mg/dl was achieved. Patients at target were asked to repeat the laboratory assessment in 3 months. At that time, patients still at target were discharged from the clinic and instructed to continue their medications and follow up with their primary care physician. Those not at target were either restarted on their ULT or it was titrated and the level re-tested in 2 weeks. Patients remained in the gout management program until they demonstrated 2 sUAs ≤ 6 mg/dl at least 3 months apart.

Pharmacological treatments

ULT was initiated with allopurinol in all patients as first-line therapy unless the patient had a known ADR or allergy to allopurinol. The starting dose for allopurinol-naïve patients was 100 mg daily (some patients were on higher doses at the time of referral). Dose titration for patients not at target sUA was done using 100 mg per day increments, or in some cases, although selected patients on 300 mg daily were titrated to 450 mg daily. The maximum allopurinol dose used in the program was 600 mg per day. Patients already on febuxostat or probenecid were maintained on these and doses titrated as needed based on sUA. Patients who developed a significant ADR or symptoms of allergy to allopurinol were switched to either febuxostat 40 mg daily or probenecid 500

mg daily, depending on their clinical status in consultation with the rheumatologist. Dose titration was then continued with these drugs if needed.

Gout-flare prophylaxis was used in all patients and in most instances we utilized colchicine 0.6 mg daily. For patients with eGFR less than 30, the dose was reduced to 0.3 mg per day. In some patients, if recommended by the rheumatologist, a daily nonsteroidal anti-inflammatory drug (NSAID) treatment was substituted, if no contraindication prevented this.

Acute gout flares were managed by the clinical pharmacist, in consultation with the rheumatologist, using oral NSAIDS, prednisone or colchicine.

Adverse drug reactions (ADR) to medications, incident gout flares and abnormal laboratory parameters were recorded by the clinical pharmacist at each telephone encounter and reviewed by the rheumatologist for management.

Results

Patient demographics and co morbidities of the pilot sample are described in Table 1.

Table 1. Demographic and clinical characteristics of patients (N=100)

Characteristic

	Mean (range)
Age, years	61 (32-94)

BMI, kg/m^2	31 (20-48)
	Percent
Male	75%
Hypertension	75%
Chronic kidney disease (CKD 2-4)	29%
Diabetes	29%
Coronary artery disease	10%
Congestive heart failure	11%
2 or more co-morbidities	46%

Three-fourths of the patients were male. The mean age was 61 years, (range: 32 – 94 years). The mean body mass index was 31 kg/m^2 (range: 20 – 48 kg/m^2). Common gout-associated co-morbidities were determined based on the presence of specific ICD-9 codes listed in the problem list of each patient in the electronic medical record, and verified by chart review. The majority of patients had at least one of the common co-morbidities associated with gout. Seventy-eight percent had hypertension, and 29% had chronic kidney disease (CKD). Of these, 2 had stage 2 CKD, 22 had stage 3 CKD and 3 had stage 4 CKD ~~stage 3 or 4~~. ~~,~~ Another ~~and~~ 29% had diabetes. A smaller number had either coronary artery disease or congestive heart failure. Forty-five percent of the patients had 2 or more of these co-morbid conditions.

Figure 2 is a schematic that shows the current status of the first 100 patients referred to our clinic. Five patients declined to participate when initially contacted by the pharmacist. Thus, 95 patients started the program, and at the time of this analysis, 78 had completed the program with 2 consecutive sUA measurements of < 6.0 mg/dl, and 4 were

still being managed. Thirteen patients left the program prior to achieving the end point. Of these, 2 patients died while in the program. One died from complications of abdominal surgery and the other, aged 94, died at home of "natural causes". One patient developed symptoms of an allergic reaction to allopurinol and declined further treatment. One patient lost insurance coverage, and another was incarcerated. The remaining 8 patients were discharged by the program pharmacist because of a pattern of non-adherence to treatment or lab monitoring, or because they elected not to complete the program. The time patients spent under program management varied considerably. The mean duration of participation was 47.8 weeks (range 14.9-109.6 weeks). Although our program was a feasibility study and designed as a short term intervention, when we examined the medical records of the 78 patients who have successfully completed the program, we found that 63 of these had been tested at least one time by their regular physician after clinic discharge (mean follow up time 36 weeks) and that 53 of these (80%) still maintained a sUA of 6.0 or less.

Figure 3 shows the sUA's of each patient in the pilot gout-management study as a set of paired samples. Each pair of bars represents the baseline sUA (red bars) and final sUA (blue bars) for each patient. For those patients still in the program (i.e., those who have not yet achieved the discharge criterion of 2 consecutive sUA measurements of $\leq$ 6.0 mg/dl), the blue bar is the most recent sUA available if the patient did not complete the program. The dotted horizontal line represents the sUA target of 6.0 mg/dl. The figure shows all the patients who entered the program, including those who are still being managed and those who did not complete the program.

To provide a more detailed view of how patients responded to management by the clinic, we plotted sequential sUA levels in a subset of our patients. Figure 4 shows this analysis in 20 randomly selected patients entering the program. Each line represents the sequential sUA measurements of a single patient for a period of 12 months. Essentially all the patients in this random sample initially responded with significant reduction in sUA. In many patients, this improvement was sustained, but in others, the sUA subsequently rose due to discontinuation of ULT. In these patients, the pharmacist was able, in most cases, to restart ULT and continue testing to assure continuing medication adherence. The Figure also shows that by 12 months in the program, 16 of the 20 patients had achieved a target sUA and two had a normal sUA of < 6.8 mg/dl.

Analysis of the 78 patients who have completed the program after achieving and maintaining the targeted sUA showed that 68 (87%, 95% CI: 78% to 94%) were on allopurinol at discharge. Figure 5 shows the distribution of allopurinol doses required to achieve a sUA of $\leq$ 6.0. The mean daily allopurinol dose required to achieve a sUA of $\leq$ 6 was 311 mg. Sixty-eight percent of patients on allopurinol achieved target on 300 mg per day or less. Only three patients achieved goal on the starting dose of 100 mg daily and two patients required 600 mg per day. All five patients on febuxostat had achieved the goal sUA level on 40 mg per day.

Three patients (3%) experienced rash or other symptoms of allergy to allopurinol. None required more than discontinuation of the medication. Of these, two patients were

changed to alternative ULT and one patient declined further treatment and discontinued the program. Elevation of ALT was seen at some time during treatment in 47 patients (48%), but only 7 of the patients had elevations high enough to require changing medication. Most stabilized or returned to normal with continued treatment and monitoring. Incident acute gout flares were reported in 33 patients (34%). None resulted in discontinuation of ULT. Gastrointestinal side effects were uncommon and in no case required a change in therapy.

Discussion

Gout is arguably the best understood of the common inflammatory arthritic diseases; effective preventive therapy is readily available and the key outcome (sUA < 6 mg/dl in most cases) is easily measured. Why, then, is unsuccessful control of sUA so frequent? A number of factors contribute to suboptimal gout management. (11,12,14) Adherence to ULT is poor when compared to medication adherence in other chronic conditions. (15) Symptoms are typically intermittent with extended gout-free periods. Moreover, there are effective treatments for gout flares, and medications (for example, colchicine) that can reduce the incidence of flares without lowering sUA. It is not surprising therefore, that many gout patients are never started on, or discontinue ULT. Another important feature of gout management is that initiation of ULT can lead to a short-term increase in incidence of gout flares, (16) further discouraging the continuation of therapy. Better patient education could be expected to improve long-term medication adherence, but is not consistently provided. (17) While diet is clearly a factor in the development of gout

(18), patients and physicians frequently place a disproportionate emphasis on dietary restrictions. (19) Although consensus guidelines recommend treating with ULT to a target sUA of 6.0 mg/dl or less, concerns about allopurinol toxicity may discourage some physicians from achieving this goal. In particular, limiting doses of allopurinol in patients with CKD lead to a high percentage of treatment failures (20). Finally, many clinical laboratories do not correctly identify serum urate concentrations of > 6.8 mg/dl as being abnormal. This leads to under-treatment and considerable confusion about diagnosis and management. (21)

Our pilot program was conceived as a way to re-frame the approach to gout management. We hypothesized that using a structured treat-to-target approach with regular monitoring and a goal-directed intervention would result in a high percentage of patients achieving a target sUA. In particular, the protocol was designed to use a slow titration of ULT along with flare prophylaxis and scheduled follow up calls. We also required sustained control of sUA for at least 3 months as a way to promote longer term medication adherence. We realize that maintaining treatment for 3 months does not guarantee long term control of sUA. Nevertheless, of the patients for whom a follow up test was available, 80% were still at target a mean of 36.8 weeks after clinic discharge. As for any chronic condition, optimal outcomes will require some level of structured monitoring.

The results of our pilot program suggest that a structured program may be an effective approach to gout management. ULT medications are highly effective, and therefore almost all our patients responded with significant reductions in sUA within weeks of

starting the program (Figure 4). Dose titration allowed most patients to achieve a target sUA of ≤ 6.0 mg/dl and to-date, all patients have been able to achieve goal using standard doses of available medications. The demographic and clinical features of the patients in our gout sample were similar to those seen in the general population of gout patients described in previous studies, (22,~~23~~) suggesting that our findings should be generalizable to gout populations outside KPNC. A nurse-staffed case management approach has been used and achieved impressive results in controlling sUA in gout patients (23~~4~~). Our pilot program is also based on a structured management approach, but did not require any clinic visits. This model is highly efficient and therefore suitable for managing a large population of gout patients, but not necessarily more effective than a case management approach.~~-~~

There is ample evidence that therapeutic inertia contributes to inadequate results of ULT (24). Our program was designed specifically to counter this problem by including repeated sUA measurements and specified actions based on the results. In addition, our protocol ~~We used a treat-to-target approach and~~ did not limit doses of allopurinol specifically based on renal function, which has been one of several impediments noted in the literature to successful ULT. Current recommendations do not support the need to limit allopurinol doses to 100 mg daily in patients with CKD, (25–27) though a low starting dose and slow titration is recommended. (26,28) Indeed, limiting the dose of allopurinol based on the presence of chronic kidney disease has been shown to result in treatment failure in an unacceptably high percentage of patients. (17) Our data confirm this observation: only three of 68 allopurinol-treated patients (4%) completing the

program achieved a sUA of ≤6.0 on 100 mg daily of allopurinol, and only 68% achieved target with 300 mg daily (Figure 5).

Not surprisingly, we encountered many cases of medication non-adherence. In most cases, this was detected in the course of the routine testing that comprised the protocol. Typically a patient whose sUA was at or near target, had a repeat test that was no longer at target. In some cases, non-adherence was discovered at the time the patient called to pharmacist because of a gout flare. Our protocol, by requiring two consecutive target sUA levels three months apart, was designed with the expectation that adherence to ULT would be inconsistent. ~~We do~~As noted previously, we do not know whether our time-limited intervention will ultimately lead to long-term control of sUA in these patients, but we were able to detect medication non-adherence in the first few months and thus reinforce the importance of long-term ULT. Ideally, monitoring of sUA would continue on a regular basis, as recommended for relevant laboratory parameters in other chronic conditions. Despite the fact that all patients were prescribed colchicine or NSAIDs for flare prophylaxis, we encountered a substantial number of gout flares during the program. While some increase in flares may be expected, in our experience, many of the flares in our patients occurred in connection with medication non-adherence. This tendency of gout patients to discontinue ULT accounted for the wide range of times patients had to stay under management. We provided our patients with written educational material as well, but could not evaluate the effectiveness of this.

We designed our pilot to be efficient and cost-effective by leveraging physician time.

The gout management program, while supervised by a rheumatologist, was staffed by a clinical pharmacist who was carefully trained in the management protocol. The pharmacist was able to manage a cohort of up to about 80 patients at a time while spending only about 6-8 hours per week. The time spent in overseeing and assisting the clinical pharmacist was never more than about 30 minutes per week for the rheumatologist once the program was in place. Moreover, our program did not require any in-person visits. This model suggests a path to improved outcomes in gout patients without generating the magnitude of increased utilization of health care resources that might otherwise be required. We recognize that pharmacists may not be available or allowed to manage patients as was done in our protocol. Even so, a trained clinical nurse could be substituted in the pharmacist's role and provide excellent care while leveraging physician time.

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Figures

Fig. 1 Clinic monitoring and treatment flow diagram

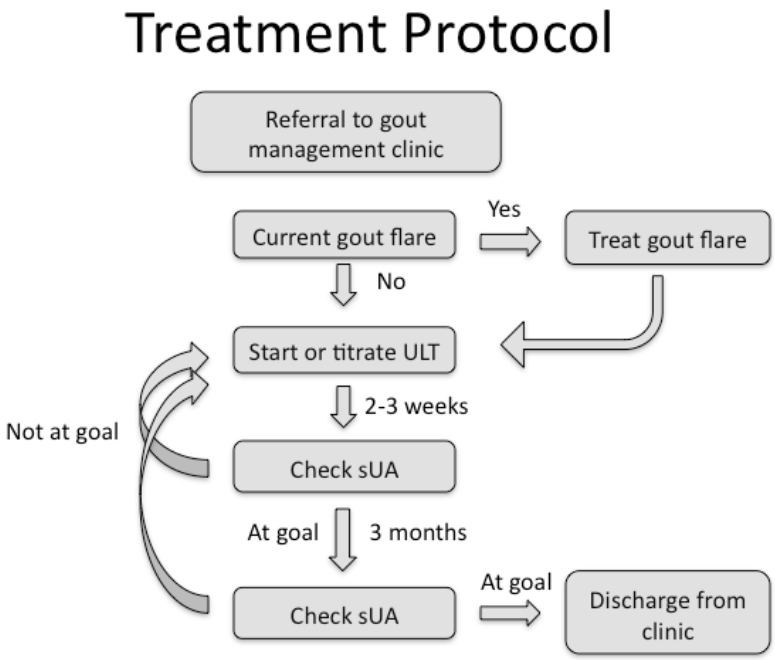


Fig. 2 Current status of first 100 patients referred to program

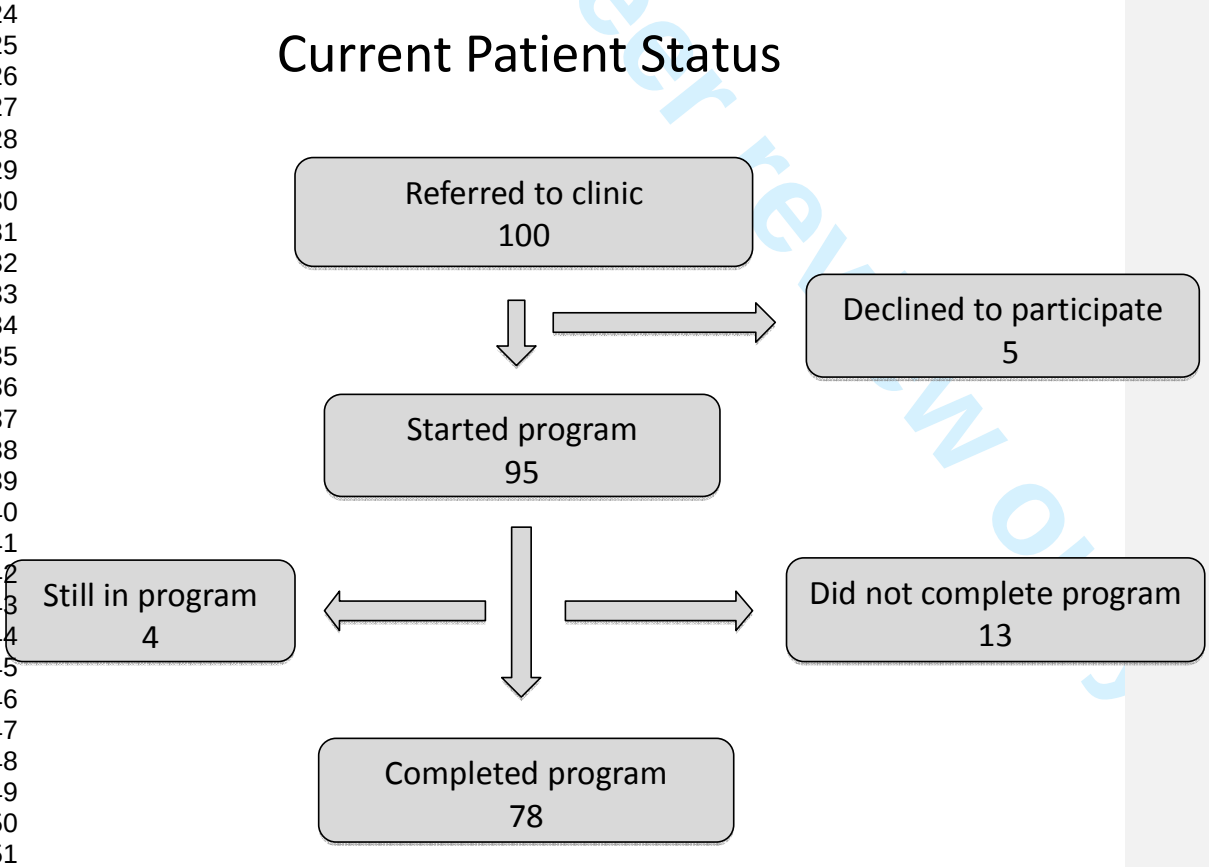


Fig. 3 Comparison of pre-treatment sUA and most recent or final sUA. Each patient is represented by a red bar (initial sUA) and a blue bar (final sUA, whether or not he/she completed the program).

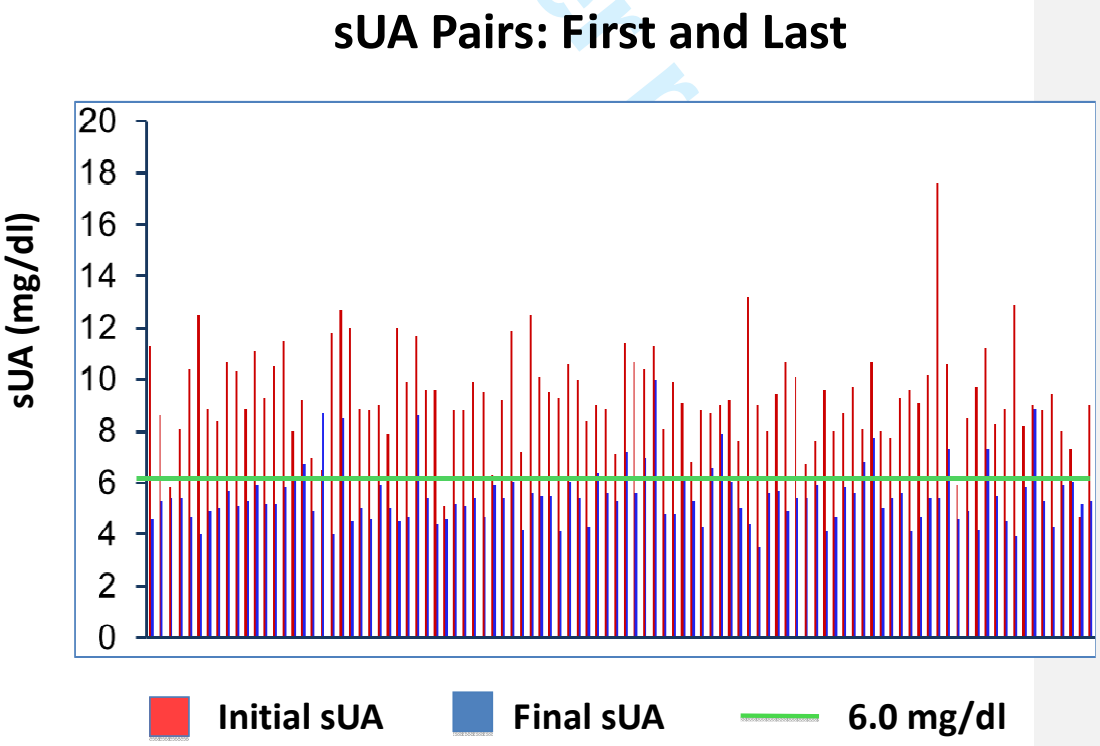


Fig. 4 sUA trend lines for 20 randomly selected patients. Each colored line represents sequential sUA levels in a single patient. Each line stops at the time of clinic discharge or is the most recent sUA if the patient had not completed or left the program.

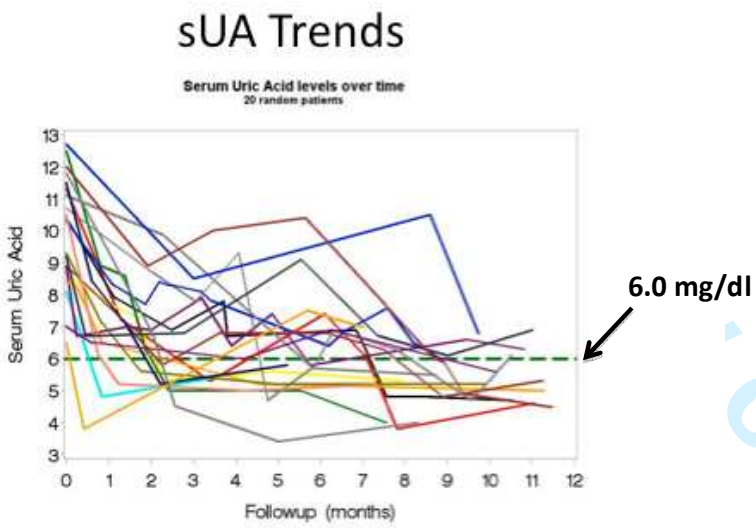
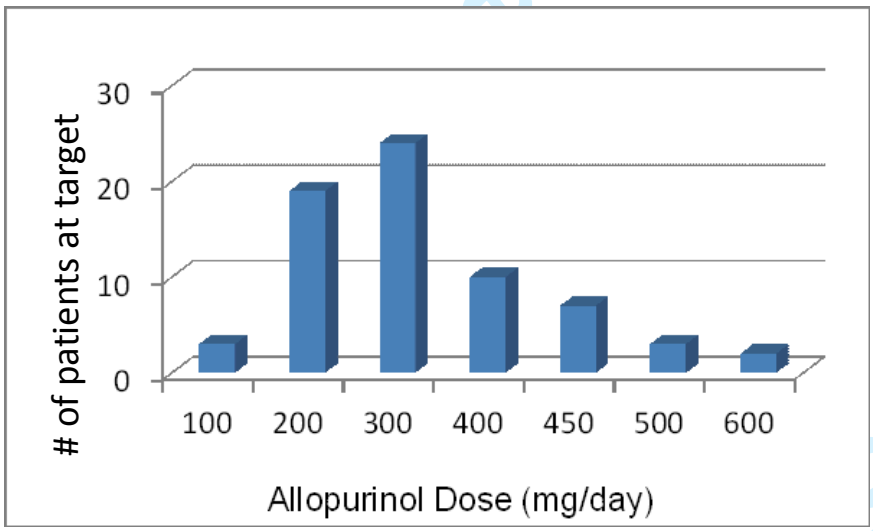


Fig. 5 Dose of Allopurinol required to achieve a sUA of ≤ 6.0 mg/dl



Effectiveness of a pharmacist-based gout care management program in a large integrated health plan: Results from a pilot study

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Effectiveness of a pharmacist-based gout care management program in a large integrated health plan: Results from a pilot study

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Abstract

Objectives:

The study objective was to determine the feasibility of using a pharmacist-staffed, protocol-based structured approach to improving the management of chronic, recurrent gout.

Setting:

The study was carried out in the outpatient clinic of a single Kaiser Permanente medical center. This is a community based clinic.

Participants:

We report on one hundred consecutive patients between the ages of 21 and 94 (75% male) with chronic or recurrent gout, referred by their primary physicians for the purpose of management of urate lowering therapy. Patients with Stage 5 chronic kidney disease or end-stage kidney disease were excluded.

Interventions:

The program consisted of a trained clinical pharmacist and a rheumatologist. The pharmacist contacted each patient by phone, provided educational and dietary materials, and used a protocol that employs standard gout medications to achieve and maintain a serum uric acid (sUA) level of 6.0 mg/dl or less. Incident gout flares or adverse reactions to medications were managed in consultation with the rheumatologist.

Primary outcome measure:

The primary outcome measure was the achievement and maintenance of a serum uric acid of 6.0 or less for a period of at least 3 months.

Results:

In 95 evaluable patients enrolled in our pilot program, a sUA of 6.0 mg/dl or less was achieved and maintained in 78 patients with 4 still in the program to date. Five patients declined to participate after referral, and another 13 patients did not complete the program. (The majority of these were due to non-adherence.)

Conclusions:

A structured pharmacist-staffed program can effectively and safely lower and maintain uric acid

levels in a high percentage of patients with recurrent gout in a primary care setting. This care model is simple to implement, efficient and warrants further validation in a clinical trial.

Article Summary

1. Article focus: Hypotheses addressed

- A structured, goal-directed program is effective in achieving optimal control of serum uric acid levels in patients with recurrent gout.
- Successful management of recurrent gout can employ a leveraged approach using a pharmacist-staffed protocol with supervision by a rheumatologist.
- Chronic gout can be managed efficiently, safely and cost-effectively using a telephone-based 'virtual clinic'.

2. Key messages

- A protocol based, goal directed gout management program is highly effective in achieving and maintaining serum uric acid control in patients with recurrent gout.
- Effective urate lowering therapy can be achieved in a high percentage of gout patients using approved doses of allopurinol when dose titration is used.
- This program appears to be a promising approach to improving gout management and may offer significant efficiency compared to current practice.

3. Strengths and Limitations

Strengths: The population we studied is representative of gout patients seen in general rheumatology practice, and therefore our results should be widely generalizable. Our program is relatively easy to implement and requires only a trained clinical pharmacist and rheumatologist to carry out.

Limitations: Although encouraging, this pilot study does not prove that our gout management program is more effective than usual care for gout because there was no control group. A study testing this hypothesis is needed. The structure of our organization, which integrates the health plan, pharmacy programs and physician care, is optimal for the use of our program. A non-integrated system might lead to barriers in setting up a similar collaboration. This may limit the applicability of the model.

Introduction

Gout is the most common inflammatory arthritis in men (1) and results in considerable morbidity and utilization of health care resources. (2) The past 30 years have witnessed a steady increase in the prevalence of gout. (3–5) The causes of this rise in gout prevalence appear to be linked to the increasing prevalence of obesity, diabetes, chronic renal disease and hypertension. (6,7) Unlike other common rheumatic diseases, the underlying cause of gout, chronic elevation of serum uric acid (sUA), is well understood.

Current approaches for management of other common chronic conditions, such as diabetes, are based on the principle that chronic illnesses are best managed by identifying predictors of optimal outcomes, setting treatment targets, and then monitoring for success in treating to the targets. (8) In the case of gout, an appropriate treatment target has been identified by expert panels sponsored by the European League Against Rheumatism (EULAR) (9) and the American College of Rheumatology (ACR). (10) Both recommend that patients with tophaceous or recurrent gout be treated with urate-lowering therapy (ULT) to a target sUA of < 6.0 mg/dl. Unfortunately, only a minority of gout patients receives appropriate treatment, including doses of ULT sufficient to achieve this target. (11) There are several reasons for this deficiency which have been addressed by other authors. (12,13). The reasons cited have included lack of appropriate monitoring, failure to treat to target and fear of escalation of ULT in some patients, particularly patients with chronic kidney disease. Taken together, it appears that there is a great need for improved approaches to the management of gout.

To address the problem of inadequate management of gout, we developed a model for gout management consisting of a 'virtual' clinic comprised of a clinical pharmacist under the supervision of a board-certified rheumatologist. Following a written protocol, the pharmacist initiates, adjusts and monitors the use of standard gout medications for patients referred by their primary care physicians for recurrent or tophaceous gout. Patients are followed by the clinic until they have 2 consecutive target sUA results at least 3 months apart, and are then discharged back to their usual care. We report here the results of a pilot program by presenting the outcomes of the first 100 patients referred to the program. Though a limited intervention, our intent was to address some of the issues identified in the literature and do it in a way that is highly leveraged and potentially suitable for a large majority of patients with chronic gout who are currently not being adequately managed.

Methods

Patient referral

Patients with gout whose primary care physicians practice at KPNC in Richmond, CA were eligible for referral to the gout management program. Referral was at the discretion of the primary care physician (sometimes in consultation with a rheumatologist), based on a history of recurrent or tophaceous gout and the intent to use urate-lowering therapy (ULT). Referring physicians were offered the choice of referring each patient for a formal rheumatology consultation, or to the gout management program, supervised by the same rheumatologist (RG). The clinical pharmacist then telephoned the referred patients,

introduced them to the protocol and, if they agreed to participate, entered them into the program. Patients consenting to treatment in the program were provided written educational material including dietary guidelines at the time of program entry. Patients with end stage renal disease were excluded from the program. The pharmacist, under a protocol approved by the Kaiser Permanente East Bay Pharmacy and Therapeutics Committee, was authorized to order relevant laboratory tests and initiate or change orders for the medications used to manage sUA, and for flare prophylaxis. For treatment of acute flares, medication orders were sometimes provided by the rheumatologist if outside the scope of the pharmacy protocol.

Laboratory assessment and monitoring

Baseline laboratory assessment performed on all referred patients consisted of a sUA, alanine aminotransferase (ALT), estimated glomerular filtration rate (eGFR) and complete blood count (CBC). This same panel of laboratory tests was repeated as needed to monitor progress while the patient was enrolled in the gout management clinic.

Treatment protocol

Figure 1 is a schematic diagram of the assessment and treatment protocol. Once entered into the program, baseline laboratory assessment was performed if not available within the prior month. If, at the time of referral, a patient was being treated for an acute flare of gout, this treatment was continued and completed. Once a baseline laboratory assessment was available, ULT was either initiated or adjusted if the sUA was above 6.0 mg/dl. Flare prophylaxis was used in all cases (see below). After any change in ULT, the patient was

instructed to return for laboratory assessment (sUA, ALT, CBC, eGFR) in 2 weeks, and report any adverse drug reactions (ADRs) or gout symptoms. ADRs or gout flares were managed by the clinical pharmacist, usually in consultation with the supervising rheumatologist. This process was continued in an iterative fashion until a target sUA of ≤ 6.0 mg/dl was achieved. Patients at target were asked to repeat the laboratory assessment in 3 months. At that time, patients still at target were discharged from the clinic and instructed to continue their medications and follow up with their primary care physician. Those not at target were either restarted on their ULT or it was titrated and the level re-tested in 2 weeks. Patients remained in the gout management program until they demonstrated 2 sUAs ≤ 6 mg/dl at least 3 months apart.

Pharmacological treatments

ULT was initiated with allopurinol in all patients as first-line therapy unless the patient had a known ADR or allergy to allopurinol. The starting dose for allopurinol-naïve patients was 100 mg daily (some patients were on higher doses at the time of referral). Dose titration for patients not at target sUA was done using 100 mg per day increments, or in some cases, although selected patients on 300 mg daily were titrated to 450 mg daily. The maximum allopurinol dose used in the program was 600 mg per day. Patients already on febuxostat or probenecid were maintained on these and doses titrated as needed based on sUA. Patients who developed a significant ADR or symptoms of allergy to allopurinol were switched to either febuxostat 40 mg daily or probenecid 500 mg daily, depending on their clinical status in consultation with the rheumatologist. Dose titration was then continued with these drugs if needed.

Gout-flare prophylaxis was used in all patients and in most instances we utilized colchicine 0.6 mg daily. For patients with eGFR less than 30, the dose was reduced to 0.3 mg per day. In some patients, if recommended by the rheumatologist, a daily nonsteroidal anti-inflammatory drug (NSAID) treatment was substituted, if no contraindication prevented this.

Acute gout flares were managed by the clinical pharmacist, in consultation with the rheumatologist, using oral NSAIDS, prednisone or colchicine.

Adverse drug reactions (ADR) to medications, incident gout flares and abnormal laboratory parameters were recorded by the clinical pharmacist at each telephone encounter and reviewed by the rheumatologist for management.

Results

Patient demographics and co morbidities of the pilot sample are described in Table 1.

Table 1. Demographic and clinical characteristics of patients (N=100)

Characteristic

	Mean (range)
Age, years	61 (32-94)
BMI, kg/m^2	31 (20-48)
	Percent
Male	75%

Hypertension	75%
Chronic kidney disease (CKD 2-4)	29%
Diabetes	29%
Coronary artery disease	10%
Congestive heart failure	11%
2 or more co-morbidities	46%

Three-fourths of the patients were male. The mean age was 61 years, (range: 32 – 94 years). The mean body mass index was 31 kg/m^2 (range: 20 – 48 kg/m^2). Common gout-associated co-morbidities were determined based on the presence of specific ICD-9 codes listed in the problem list of each patient in the electronic medical record, and verified by chart review. The majority of patients had at least one of the common co-morbidities associated with gout. Seventy-eight percent had hypertension, and 29% had chronic kidney disease (CKD). Of these, 2 had stage 2 CKD, 22 had stage 3 CKD and 3 had stage 4 CKD. Another 29% had diabetes. A smaller number had either coronary artery disease or congestive heart failure. Forty-five percent of the patients had 2 or more of these co-morbid conditions.

Figure 2 is a schematic that shows the current status of the first 100 patients referred to our clinic. Five patients declined to participate when initially contacted by the pharmacist. Thus, 95 patients started the program, and at the time of this analysis, 78 had completed the program with 2 consecutive sUA measurements of < 6.0 mg/dl, and 4 were still being managed. Thirteen patients left the program prior to achieving the end point. Of these, 2 patients died while in the program. One died from complications of abdominal surgery and the other, aged 94, died at home of "natural causes". One patient

developed symptoms of an allergic reaction to allopurinol and declined further treatment. One patient lost insurance coverage, and another was incarcerated. The remaining 8 patients were discharged by the program pharmacist because of a pattern of non-adherence to treatment or lab monitoring, or because they elected not to complete the program. The time patients spent under program management varied considerably. The mean duration of participation was 47.8 weeks (range 14.9-109.6 weeks). Although our program was a feasibility study and designed as a short term intervention, when we examined the medical records of the 78 patients who have successfully completed the program, we found that 63 of these had been tested at least one time by their regular physician after clinic discharge (mean follow up time 36 weeks) and that 53 of these (80%) still maintained a sUA of 6.0 or less.

Figure 3 shows the sUA's of each patient in the pilot gout-management study as a set of paired samples. Each pair of bars represents the baseline sUA (red bars) and final sUA (blue bars) for each patient. For those patients still in the program (i.e., those who have not yet achieved the discharge criterion of 2 consecutive sUA measurements of $\leq$ 6.0 mg/dl), the blue bar is the most recent sUA available if the patient did not complete the program. The dotted horizontal line represents the sUA target of 6.0 mg/dl. The figure shows all the patients who entered the program, including those who are still being managed and those who did not complete the program.

To provide a more detailed view of how patients responded to management by the clinic, we plotted sequential sUA levels in a subset of our patients. Figure 4 shows this analysis

in 20 randomly selected patients entering the program. Each line represents the sequential sUA measurements of a single patient for a period of 12 months. Essentially all the patients in this random sample initially responded with significant reduction in sUA. In many patients, this improvement was sustained, but in others, the sUA subsequently rose due to discontinuation of ULT. In these patients, the pharmacist was able, in most cases, to restart ULT and continue testing to assure continuing medication adherence. The Figure also shows that by 12 months in the program, 16 of the 20 patients had achieved a target sUA and two had a normal sUA of < 6.8 mg/dl.

Analysis of the 78 patients who have completed the program after achieving and maintaining the targeted sUA showed that 68 (87%, 95% CI: 78% to 94%) were on allopurinol at discharge. Figure 5 shows the distribution of allopurinol doses required to achieve a sUA of $\leq$ 6.0. The mean daily allopurinol dose required to achieve a sUA of $\leq$ 6 was 311 mg. Sixty-eight percent of patients on allopurinol achieved target on 300 mg per day or less. Only three patients achieved goal on the starting dose of 100 mg daily and two patients required 600 mg per day. All five patients on febuxostat had achieved the goal sUA level on 40 mg per day.

Three patients (3%) experienced rash or other symptoms of allergy to allopurinol. None required more than discontinuation of the medication. Of these, two patients were changed to alternative ULT and one patient declined further treatment and discontinued the program. Elevation of ALT was seen at some time during treatment in 47 patients (48%), but only 7 of the patients had elevations high enough to require changing

medication. Most stabilized or returned to normal with continued treatment and monitoring. Incident acute gout flares were reported in 33 patients (34%). None resulted in discontinuation of ULT. Gastrointestinal side effects were uncommon and in no case required a change in therapy.

Discussion

Gout is arguably the best understood of the common inflammatory arthritic diseases; effective preventive therapy is readily available and the key outcome (sUA < 6 mg/dl in most cases) is easily measured. Why, then, is unsuccessful control of sUA so frequent? A number of factors contribute to suboptimal gout management. (11,12,14) Adherence to ULT is poor when compared to medication adherence in other chronic conditions. (15) Symptoms are typically intermittent with extended gout-free periods. Moreover, there are effective treatments for gout flares, and medications (for example, colchicine) that can reduce the incidence of flares without lowering sUA. It is not surprising therefore, that many gout patients are never started on, or discontinue ULT. Another important feature of gout management is that initiation of ULT can lead to a short-term increase in incidence of gout flares, (16) further discouraging the continuation of therapy. Better patient education could be expected to improve long-term medication adherence, but is not consistently provided. (17) While diet is clearly a factor in the development of gout (18), patients and physicians frequently place a disproportionate emphasis on dietary restrictions. (19) Although consensus guidelines recommend treating with ULT to a target sUA of 6.0 mg/dl or less, concerns about allopurinol toxicity may discourage some

physicians from achieving this goal. In particular, limiting doses of allopurinol in patients with CKD lead to a high percentage of treatment failures (20). Finally, many clinical laboratories do not correctly identify serum urate concentrations of > 6.8 mg/dl as being abnormal. This leads to under-treatment and considerable confusion about diagnosis and management. (21)

Our pilot program was conceived as a way to re-frame the approach to gout management. We hypothesized that using a structured treat-to-target approach with regular monitoring and a goal-directed intervention would result in a high percentage of patients achieving a target sUA. In particular, the protocol was designed to use a slow titration of ULT along with flare prophylaxis and scheduled follow up calls. We also required sustained control of sUA for at least 3 months as a way to promote longer term medication adherence. We realize that maintaining treatment for 3 months does not guarantee long term control of sUA. Nevertheless, of the patients for whom a follow up test was available, 80% were still at target a mean of 36.8 weeks after clinic discharge. As for any chronic condition, optimal outcomes will require some level of structured monitoring.

The results of our pilot program suggest that a structured program may be an effective approach to gout management. ULT medications are highly effective, and therefore almost all our patients responded with significant reductions in sUA within weeks of starting the program (Figure 4). Dose titration allowed most patients to achieve a target sUA of $\leq$ 6.0 mg/dl and to-date, all patients have been able to achieve goal using standard doses of available medications. The demographic and clinical features of the patients in

our gout sample were similar to those seen in the general population of gout patients described in previous studies, (22) suggesting that our findings should be generalizable to gout populations outside KPNC. A nurse-staffed case management approach has been used and achieved impressive results in controlling sUA in gout patients (23). Our pilot program is also based on a structured management approach, but did not require any clinic visits. This model is highly efficient and therefore suitable for managing a large population of gout patients, but not necessarily more effective than a case management approach.

There is ample evidence that therapeutic inertia contributes to inadequate results of ULT (24). Our program was designed specifically to counter this problem by including repeated sUA measurements and specified actions based on the results. In addition, our protocol did not limit doses of allopurinol specifically based on renal function, which has been one of several impediments noted in the literature to successful ULT. Current recommendations do not support the need to limit allopurinol doses to 100 mg daily in patients with CKD, (25–27) though a low starting dose and slow titration is recommended. (26,28) Indeed, limiting the dose of allopurinol based on the presence of chronic kidney disease has been shown to result in treatment failure in an unacceptably high percentage of patients. (17) Our data confirm this observation: only three of 68 allopurinol-treated patients (4%) completing the program achieved a sUA of $\leq$6.0 on 100 mg daily of allopurinol, and only 68% achieved target with 300 mg daily (Figure 5).

Not surprisingly, we encountered many cases of medication non-adherence. In most

cases, this was detected in the course of the routine testing that comprised the protocol. Typically a patient whose sUA was at or near target, had a repeat test that was no longer at target. In some cases, non-adherence was discovered at the time the patient called to pharmacist because of a gout flare. Our protocol, by requiring two consecutive target sUA levels three months apart, was designed with the expectation that adherence to ULT would be inconsistent. As noted previously, we do not know whether our time-limited intervention will ultimately lead to long-term control of sUA in these patients, but we were able to detect medication non-adherence in the first few months and thus reinforce the importance of long-term ULT. Ideally, monitoring of sUA would continue on a regular basis, as recommended for relevant laboratory parameters in other chronic conditions. Despite the fact that all patients were prescribed colchicine or NSAIDs for flare prophylaxis, we encountered a substantial number of gout flares during the program. While some increase in flares may be expected, in our experience, many of the flares in our patients occurred in connection with medication non-adherence. This tendency of gout patients to discontinue ULT accounted for the wide range of times patients had to stay under management. We provided our patients with written educational material as well, but could not evaluate the effectiveness of this.

We designed our pilot to be efficient and cost-effective by leveraging physician time. The gout management program, while supervised by a rheumatologist, was staffed by a clinical pharmacist who was carefully trained in the management protocol. The pharmacist was able to manage a cohort of up to about 80 patients at a time while spending only about 6-8 hours per week. The time spent in overseeing and assisting the

clinical pharmacist was never more than about 30 minutes per week for the rheumatologist once the program was in place. Moreover, our program did not require any in-person visits. This model suggests a path to improved outcomes in gout patients without generating the magnitude of increased utilization of health care resources that might otherwise be required. We recognize that pharmacists may not be available or allowed to manage patients as was done in our protocol. Even so, a trained clinical nurse could be substituted in the pharmacist's role and provide excellent care while leveraging physician time.

Contributorship Statement

Robert Goldfien

Conceived and developed protocol and program. Participated in collection and analysis of data, and pharmacist supervision. Primary author of manuscript.

Andrew Avins

Consulted on project design, data capture, statistical methods and manuscript editing.

Alice Pressman

Oversaw data analysis and presentation. Consulted on data analysis and manuscript editing.

Alice Hwe

Oversaw development and approval of treatment protocol and supervised clinical pharmacists.

Alice Jacobson

Assisted with data collection and analysis.

Michele Ng and Goldie Yip

Worked directly with subjects to arrange data collection, adjust medications, obtain clinical information and report issues or concerns with supervising rheumatologist

Data sharing

There are no additional unpublished data from this study.

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None of the authors has any potential conflict of interest regarding this work

There is no additional data available.

Competing Interests

None.

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Figures

Fig. 1 Clinic monitoring and treatment flow diagram

Fig. 2 Current status of first 100 patients referred to program

Fig. 3 Comparison of pre-treatment sUA and most recent or final sUA. Each patient is represented by a red bar (initial sUA) and a blue bar (final sUA, whether or not he/she completed the program).

Fig. 4 sUA trend lines for 20 randomly selected patients. Each colored line represents sequential sUA levels in a single patient. Each line stops at the time of clinic discharge or is the most recent sUA if the patient had not completed or left the program.

Fig. 5 Dose of Allopurinol required to achieve a sUA of $\leq$ 6.0 mg/dl

Effectiveness of a pharmacist-based gout care management program in a large integrated health plan: Results from a pilot study

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Abstract

Background:

The incidence of gout has been steadily rising. While effective treatments are available, treatment is often unsuccessful because current approaches to management lack a systematic approach. To address this shortcoming we tested a protocol-based, pharmacist-staffed intervention to manage patients with recurrent gout.

Methods:

Patients in Kaiser Permanente, Northern California (KPNC) with recurrent gout were referred by their primary care physicians to a pharmacist-staffed gout management clinic supervised by a board-certified rheumatologist. The pharmacist used a protocol that employs standard gout medications to achieve and maintain a serum uric acid (sUA) level of 6.0 mg/dl or less. Results from the first 100 consecutive patients enrolled in this pilot program are reported here.

Results:

In 95 evaluable patients enrolled in our pilot program, a sUA of 6.0 mg/dl or less was achieved and maintained in 78 patients with 4 still in the program to date. Five patients declined to participate after referral, and another 13 patients did not complete the program. (The majority of these were due to non-adherence.)

Conclusions:

A structured pharmacist-staffed program can effectively and safely lower and maintain uric acid levels in a high percentage of patients with recurrent gout. This care model is simple to implement, efficient and warrants further validation in a clinical trial.

Introduction

Gout is the most common inflammatory arthritis in men (1) and results in considerable morbidity and utilization of health care resources. (2) The past 30 years have witnessed a steady increase in the prevalence of gout. (3–5) The causes of this rise in gout prevalence appear to be linked to the increasing prevalence of obesity, diabetes, chronic renal disease and hypertension. (6,7) Unlike other common rheumatic diseases, the underlying cause of gout, chronic elevation of serum uric acid (sUA), is well understood.

Current approaches for management of other common chronic conditions, such as diabetes, are based on the principle that chronic illnesses are best managed by identifying predictors of optimal outcomes, setting treatment targets, and then monitoring for success in treating to the targets. (8) In the case of gout, an appropriate treatment target has been identified by expert panels sponsored by the European League Against Rheumatism (EULAR) (9) and the American College of Rheumatology (ACR). (10) Both recommend that patients with tophaceous or recurrent gout be treated with urate-lowering therapy (ULT) to a target sUA of < 6.0 mg/dl. Unfortunately, only a minority of gout patients receives appropriate treatment, including doses of ULT sufficient to achieve this target. (11) There are several reasons for this deficiency which have been addressed by other authors. (12,13). The reasons cited have included lack of appropriate monitoring, failure to treat to target and fear of escalation of ULT in some patients, particularly patients with chronic kidney disease. Taken together, it appears that there is a great need for improved approaches to the management of gout.

To address the problem of inadequate management of gout, we developed a model for gout management consisting of a 'virtual' clinic comprised of a clinical pharmacist under the supervision of a board-certified rheumatologist. Following a written protocol, the pharmacist initiates, adjusts and monitors the use of standard gout medications for patients referred by their primary care physicians for recurrent or tophaceous gout. Patients are followed by the clinic until they have 2 consecutive target sUA results at least 3 months apart, and are then discharged back to their usual care. We report here the results of a pilot program by presenting the outcomes of the first 100 patients referred to the program. Though a limited intervention, our intent was to address some of the issues identified in the literature and do it in a way that is highly leveraged and potentially suitable for a large majority of patients with chronic gout who are currently not being adequately managed.

Methods

Patient referral

Patients with gout whose primary care physicians practice at KPNC in Richmond, CA were eligible for referral to the gout management program. Referral was at the discretion of the primary care physician (sometimes in consultation with a rheumatologist), based on a history of recurrent or tophaceous gout and the intent to use urate-lowering therapy (ULT). Referring physicians were offered the choice of referring each patient for a formal rheumatology consultation, or to the gout management program, supervised by the

same rheumatologist (RG). The clinical pharmacist then telephoned the referred patients, introduced them to the protocol and, if they agreed to participate, entered them into the program. Patients consenting to treatment in the program were provided written educational material including dietary guidelines at the time of program entry. Patients with end stage renal disease were excluded from the program. The pharmacist, under a protocol approved by the Kaiser Permanente East Bay Pharmacy and Therapeutics Committee, was authorized to order relevant laboratory tests and initiate or change orders for the medications used to manage sUA, and for flare prophylaxis. For treatment of acute flares, medication orders were sometimes provided by the rheumatologist if outside the scope of the pharmacy protocol.

Laboratory assessment and monitoring

Baseline laboratory assessment performed on all referred patients consisted of a sUA, alanine aminotransferase (ALT), estimated glomerular filtration rate (eGFR) and complete blood count (CBC). This same panel of laboratory tests was repeated as needed to monitor progress while the patient was enrolled in the gout management clinic.

Treatment protocol

Figure 1 is a schematic diagram of the assessment and treatment protocol. Once entered into the program, baseline laboratory assessment was performed if not available within the prior month. If, at the time of referral, a patient was being treated for an acute flare of gout, this treatment was continued and completed. Once a baseline laboratory assessment was available, ULT was either initiated or adjusted if the sUA was above 6.0 mg/dl. Flare

prophylaxis was used in all cases (see below). After any change in ULT, the patient was instructed to return for laboratory assessment (sUA, ALT, CBC, eGFR) in 2 weeks, and report any adverse drug reactions (ADRs) or gout symptoms. ADRs or gout flares were managed by the clinical pharmacist, usually in consultation with the supervising rheumatologist. This process was continued in an iterative fashion until a target sUA of ≤ 6.0 mg/dl was achieved. Patients at target were asked to repeat the laboratory assessment in 3 months. At that time, patients still at target were discharged from the clinic and instructed to continue their medications and follow up with their primary care physician. Those not at target were either restarted on their ULT or it was titrated and the level re-tested in 2 weeks. Patients remained in the gout management program until they demonstrated 2 sUAs ≤ 6 mg/dl at least 3 months apart.

Pharmacological treatments

ULT was initiated with allopurinol in all patients as first-line therapy unless the patient had a known ADR or allergy to allopurinol. The starting dose for allopurinol-naïve patients was 100 mg daily (some patients were on higher doses at the time of referral). Dose titration for patients not at target sUA was done using 100 mg per day increments, or in some cases, although selected patients on 300 mg daily were titrated to 450 mg daily. The maximum allopurinol dose used in the program was 600 mg per day. Patients already on febuxostat or probenecid were maintained on these and doses titrated as needed based on sUA. Patients who developed a significant ADR or symptoms of allergy to allopurinol were switched to either febuxostat 40 mg daily or probenecid 500

mg daily, depending on their clinical status in consultation with the rheumatologist. Dose titration was then continued with these drugs if needed.

Gout-flare prophylaxis was used in all patients and in most instances we utilized colchicine 0.6 mg daily. For patients with eGFR less than 30, the dose was reduced to 0.3 mg per day. In some patients, if recommended by the rheumatologist, a daily nonsteroidal anti-inflammatory drug (NSAID) treatment was substituted, if no contraindication prevented this.

Acute gout flares were managed by the clinical pharmacist, in consultation with the rheumatologist, using oral NSAIDS, prednisone or colchicine.

Adverse drug reactions (ADR) to medications, incident gout flares and abnormal laboratory parameters were recorded by the clinical pharmacist at each telephone encounter and reviewed by the rheumatologist for management.

Results

Patient demographics and co morbidities of the pilot sample are described in Table 1.

Table 1. Demographic and clinical characteristics of patients (N=100)

Characteristic

	Mean (range)
Age, years	61 (32-94)

BMI, kg/m^2	31 (20-48)
	Percent
Male	75%
Hypertension	75%
Chronic kidney disease (CKD 2-4)	29%
Diabetes	29%
Coronary artery disease	10%
Congestive heart failure	11%
2 or more co-morbidities	46%

Three-fourths of the patients were male. The mean age was 61 years, (range: 32 – 94 years). The mean body mass index was 31 kg/m^2 (range: 20 – 48 kg/m^2). Common gout-associated co-morbidities were determined based on the presence of specific ICD-9 codes listed in the problem list of each patient in the electronic medical record, and verified by chart review. The majority of patients had at least one of the common co-morbidities associated with gout. Seventy-five ~~eight~~ percent had hypertension, and 29% had chronic kidney disease (CKD). Of these, 2 had stage 2 CKD, 22 had stage 3 CKD and 3 had stage 4 CKD. Another 29% had diabetes. A smaller number had either coronary artery disease or congestive heart failure. Forty-five percent of the patients had 2 or more of these co-morbid conditions.

Figure 2 is a schematic that shows the current status of the first 100 patients referred to our clinic. Five patients declined to participate when initially contacted by the pharmacist. Thus, 95 patients started the program, and at the time of this analysis, 78 had completed the program with 2 consecutive sUA measurements of < 6.0 mg/dl, and 4 were

still being managed. Thirteen patients left the program prior to achieving the end point. Of these, 2 patients died while in the program. One died from complications of abdominal surgery and the other, aged 94, died at home of "natural causes". One patient developed symptoms of an allergic reaction to allopurinol and declined further treatment. One patient lost insurance coverage, and another was incarcerated. The remaining 8 patients were discharged by the program pharmacist because of a pattern of non-adherence to treatment or lab monitoring, or because they elected not to complete the program. The time patients spent under program management varied considerably. The mean duration of participation was 47.8 weeks (range 14.9-109.6 weeks). Although our program was a feasibility study and designed as a short term intervention, when we examined the medical records of the 78 patients who have successfully completed the program, we found that 63 of these had been tested at least one time by their regular physician after clinic discharge (mean follow up time 36 weeks) and that 53 of these (80%) still maintained a sUA of 6.0 or less.

Figure 3 shows the sUA's of each patient in the pilot gout-management study as a set of paired samples. Each pair of bars represents the baseline sUA (red bars) and final sUA (blue bars) for each patient. For those patients still in the program (i.e., those who have not yet achieved the discharge criterion of 2 consecutive sUA measurements of $\leq$ 6.0 mg/dl), the blue bar is the most recent sUA available if the patient did not complete the program. The dotted horizontal line represents the sUA target of 6.0 mg/dl. The figure shows all the patients who entered the program, including those who are still being managed and those who did not complete the program.

To provide a more detailed view of how patients responded to management by the clinic, we plotted sequential sUA levels in a subset of our patients. Figure 4 shows this analysis in 20 randomly selected patients entering the program. Each line represents the sequential sUA measurements of a single patient for a period of 12 months. Essentially all the patients in this random sample initially responded with significant reduction in sUA. In many patients, this improvement was sustained, but in others, the sUA subsequently rose due to discontinuation of ULT. In these patients, the pharmacist was able, in most cases, to restart ULT and continue testing to assure continuing medication adherence. The Figure also shows that by 12 months in the program, 16 of the 20 patients had achieved a target sUA and two had a normal sUA of < 6.8 mg/dl.

Analysis of the 78 patients who have completed the program after achieving and maintaining the targeted sUA showed that 68 (87%, 95% CI: 78% to 94%) were on allopurinol at discharge. Figure 5 shows the distribution of allopurinol doses required to achieve a sUA of $\leq$ 6.0. The mean daily allopurinol dose required to achieve a sUA of $\leq$ 6 was 311 mg. Sixty-eight percent of patients on allopurinol achieved target on 300 mg per day or less. Only three patients achieved goal on the starting dose of 100 mg daily and two patients required 600 mg per day. All five patients on febuxostat had achieved the goal sUA level on 40 mg per day.

Three patients (3%) experienced rash or other symptoms of allergy to allopurinol. None required more than discontinuation of the medication. Of these, two patients were

changed to alternative ULT and one patient declined further treatment and discontinued the program. Elevation of ALT was seen at some time during treatment in 47 patients (48%), but only 7 of the patients had elevations high enough to require changing medication. Most stabilized or returned to normal with continued treatment and monitoring. Incident acute gout flares were reported in 33 patients (34%). None resulted in discontinuation of ULT. Gastrointestinal side effects were uncommon and in no case required a change in therapy.

Discussion

Gout is arguably the best understood of the common inflammatory arthritic diseases; effective preventive therapy is readily available and the key outcome (sUA < 6 mg/dl in most cases) is easily measured. Why, then, is unsuccessful control of sUA so frequent? A number of factors contribute to suboptimal gout management. (11,12,14) Adherence to ULT is poor when compared to medication adherence in other chronic conditions. (15) Symptoms are typically intermittent with extended gout-free periods. Moreover, there are effective treatments for gout flares, and medications (for example, colchicine) that can reduce the incidence of flares without lowering sUA. It is not surprising therefore, that many gout patients are never started on, or discontinue ULT. Another important feature of gout management is that initiation of ULT can lead to a short-term increase in incidence of gout flares, (16) further discouraging the continuation of therapy. Better patient education could be expected to improve long-term medication adherence, but is not consistently provided. (17) While diet is clearly a factor in the development of gout

(18), patients and physicians frequently place a disproportionate emphasis on dietary restrictions. (19) Although consensus guidelines recommend treating with ULT to a target sUA of 6.0 mg/dl or less, concerns about allopurinol toxicity may discourage some physicians from achieving this goal. In particular, limiting doses of allopurinol in patients with CKD lead to a high percentage of treatment failures (20). Finally, many clinical laboratories do not correctly identify serum urate concentrations of > 6.8 mg/dl as being abnormal. This leads to under-treatment and considerable confusion about diagnosis and management. (21)

Our pilot program was conceived as a way to re-frame the approach to gout management. We hypothesized that using a structured treat-to-target approach with regular monitoring and a goal-directed intervention would result in a high percentage of patients achieving a target sUA. In particular, the protocol was designed to use a slow titration of ULT along with flare prophylaxis and scheduled follow up calls. We also required sustained control of sUA for at least 3 months as a way to promote longer term medication adherence. We realize that maintaining treatment for 3 months does not guarantee long term control of sUA. Nevertheless, of the patients for whom a follow up test was available, 80% were still at target a mean of 36.8 weeks after clinic discharge. As for any chronic condition, optimal outcomes will require some level of structured monitoring.

The results of our pilot program suggest that a structured program may be an effective approach to gout management. ULT medications are highly effective, and therefore almost all our patients responded with significant reductions in sUA within weeks of

starting the program (Figure 4). Dose titration allowed most patients to achieve a target sUA of ≤ 6.0 mg/dl and to-date, all patients have been able to achieve goal using standard doses of available medications. The demographic and clinical features of the patients in our gout sample were similar to those seen in the general population of gout patients described in previous studies, (22) suggesting that our findings should be generalizable to gout populations outside KPNC. A nurse-staffed case management approach has been used and achieved impressive results in controlling sUA in gout patients (23). Our pilot program is also based on a structured management approach, but did not require any clinic visits. This model is highly efficient and therefore suitable for managing a large population of gout patients, but not necessarily more effective than a case management approach.

There is ample evidence that therapeutic inertia contributes to inadequate results of ULT (24). Our program was designed specifically to counter this problem by including repeated sUA measurements and specified actions based on the results. In addition, our protocol did not limit doses of allopurinol specifically based on renal function, which has been one of several impediments noted in the literature to successful ULT. Current recommendations do not support the need to limit allopurinol doses to 100 mg daily in patients with CKD, (25–27) though a low starting dose and slow titration is recommended. (26,28) Indeed, limiting the dose of allopurinol based on the presence of chronic kidney disease has been shown to result in treatment failure in an unacceptably high percentage of patients. (17) Our data confirm this observation: only three of 68 allopurinol-treated patients (4%) completing the program achieved a sUA of ≤6.0 on

100 mg daily of allopurinol, and only 68% achieved target with 300 mg daily (Figure 5).

Not surprisingly, we encountered many cases of medication non-adherence. In most cases, this was detected in the course of the routine testing that comprised the protocol. Typically a patient whose sUA was at or near target, had a repeat test that was no longer at target. In some cases, non-adherence was discovered at the time the patient called to pharmacist because of a gout flare. Our protocol, by requiring two consecutive target sUA levels three months apart, was designed with the expectation that adherence to ULT would be inconsistent. As noted previously, we do not know whether our time-limited intervention will ultimately lead to long-term control of sUA in these patients, but we were able to detect medication non-adherence in the first few months and thus reinforce the importance of long-term ULT. Ideally, monitoring of sUA would continue on a regular basis, as recommended for relevant laboratory parameters in other chronic conditions. Despite the fact that all patients were prescribed colchicine or NSAIDs for flare prophylaxis, we encountered a substantial number of gout flares during the program. While some increase in flares may be expected, in our experience, many of the flares in our patients occurred in connection with medication non-adherence. This tendency of gout patients to discontinue ULT accounted for the wide range of times patients had to stay under management. We provided our patients with written educational material as well, but could not evaluate the effectiveness of this.

We designed our pilot to be efficient and cost-effective by leveraging physician time. The gout management program, while supervised by a rheumatologist, was staffed by a

clinical pharmacist who was carefully trained in the management protocol. The pharmacist was able to manage a cohort of up to about 80 patients at a time while spending only about 6-8 hours per week. The time spent in overseeing and assisting the clinical pharmacist was never more than about 30 minutes per week for the rheumatologist once the program was in place. Moreover, our program did not require any in-person visits. This model suggests a path to improved outcomes in gout patients without generating the magnitude of increased utilization of health care resources that might otherwise be required. We recognize that pharmacists may not be available or allowed to manage patients as was done in our protocol. Even so, a trained clinical nurse could be substituted in the pharmacist's role and provide excellent care while leveraging physician time.

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Figures

Fig. 1 Clinic monitoring and treatment flow diagram

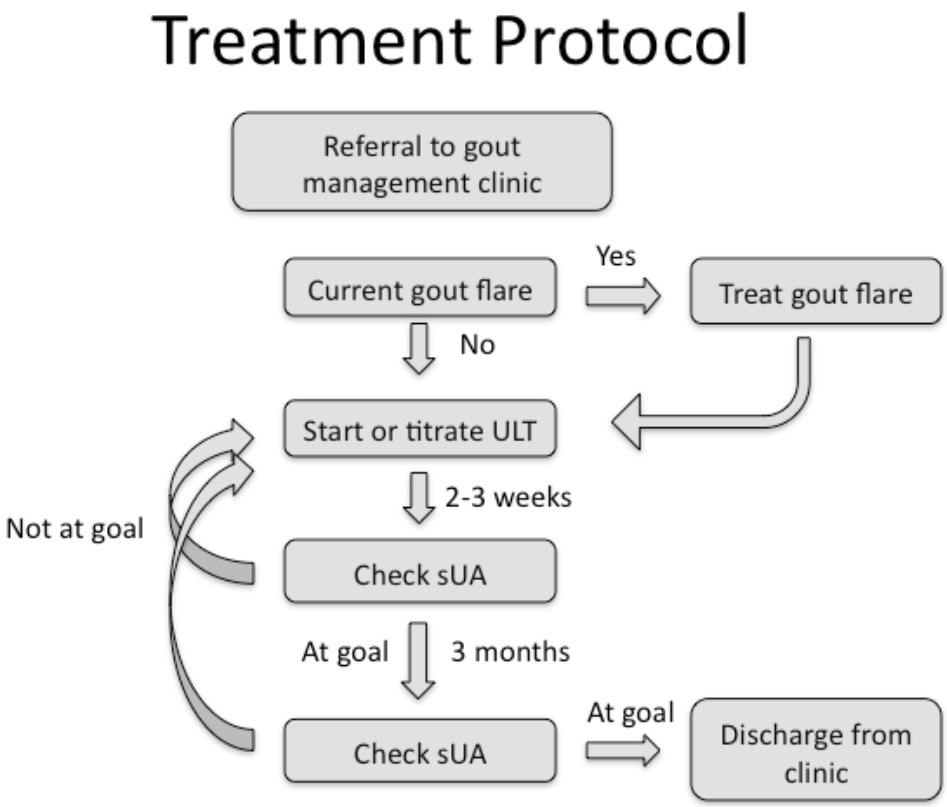


Fig. 2 Current status of first 100 patients referred to program

Current Patient Status

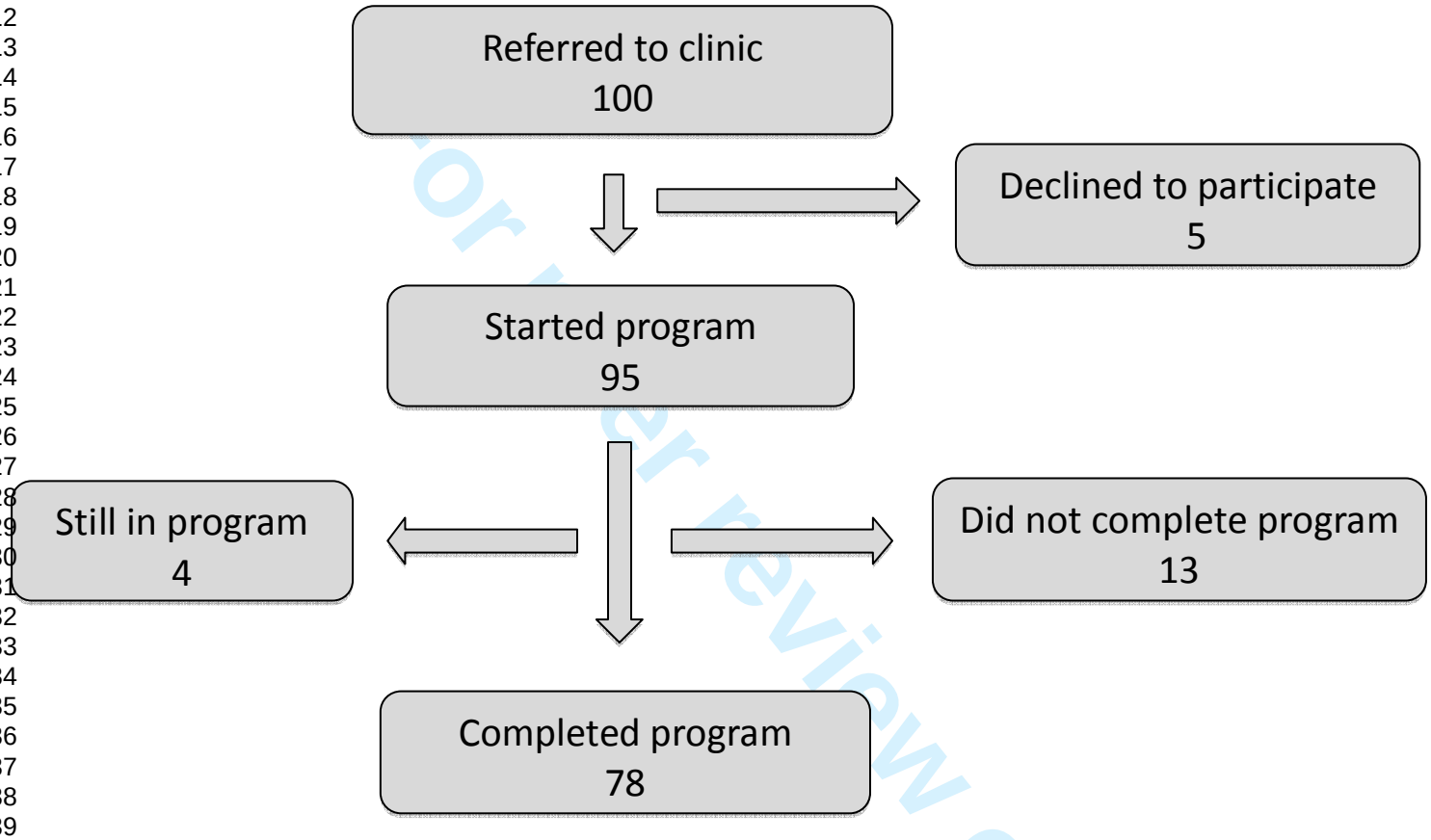


Fig. 3 Comparison of pre-treatment sUA and most recent or final sUA. Each patient is represented by a red bar (initial sUA) and a blue bar (final sUA, whether or not he/she completed the program).

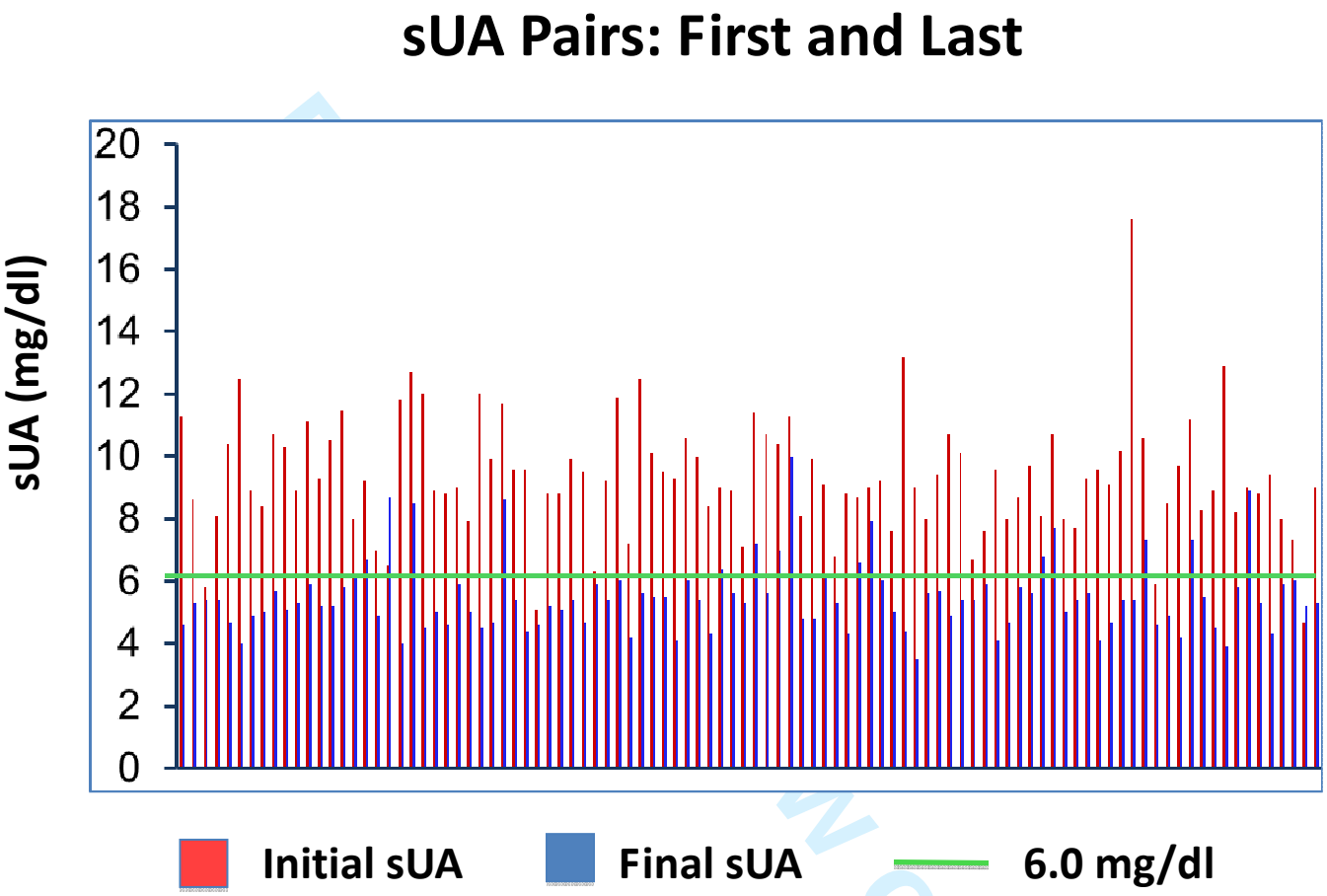


Fig. 4 sUA trend lines for 20 randomly selected patients. Each colored line represents sequential sUA levels in a single patient. Each line stops at the time of clinic discharge or is the most recent sUA if the patient had not completed or left the program.

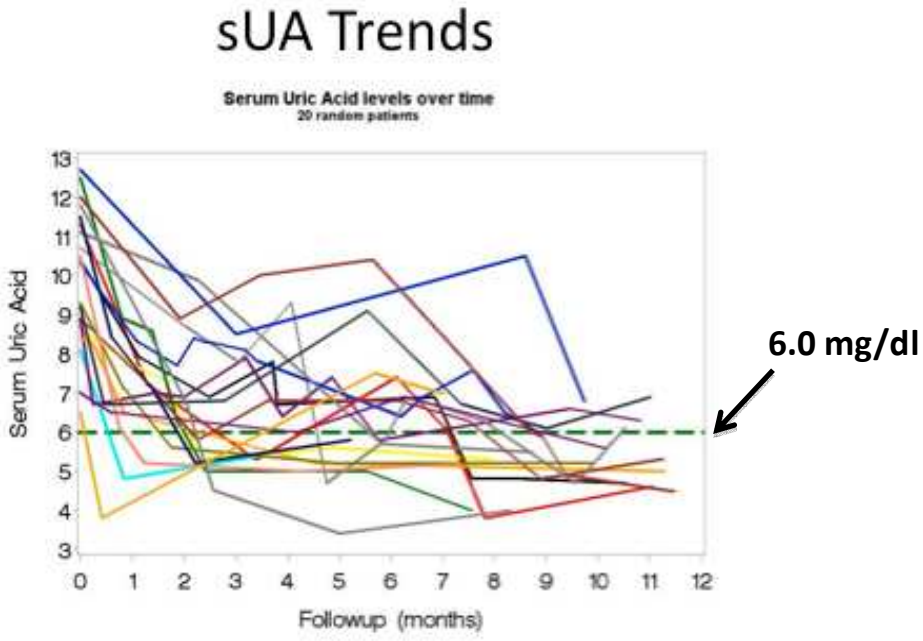
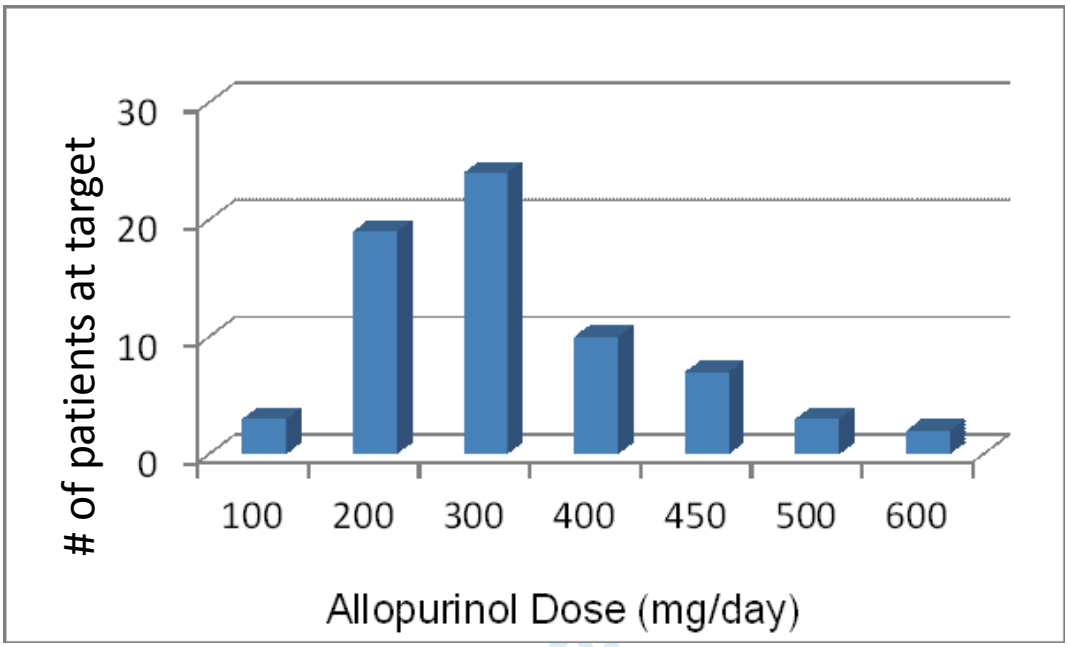
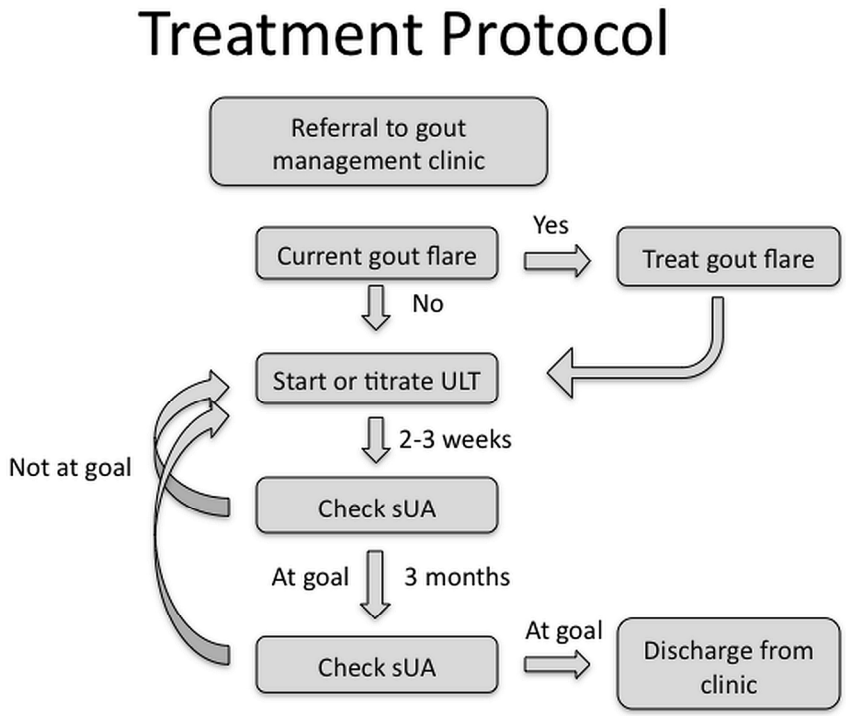
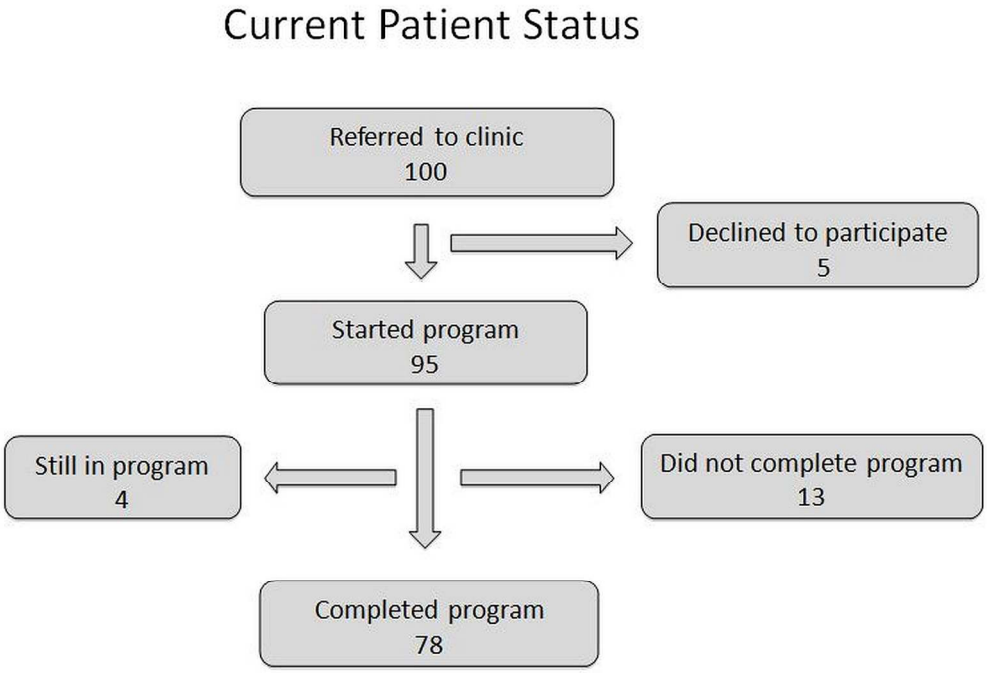


Fig. 5 Dose of Allopurinol required to achieve a sUA of ≤ 6.0 mg/dl







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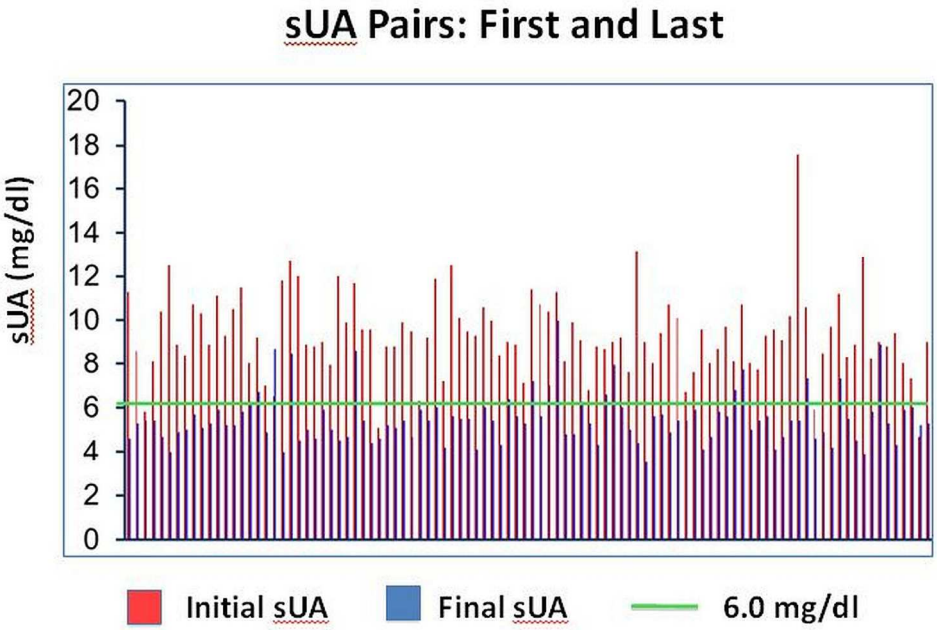

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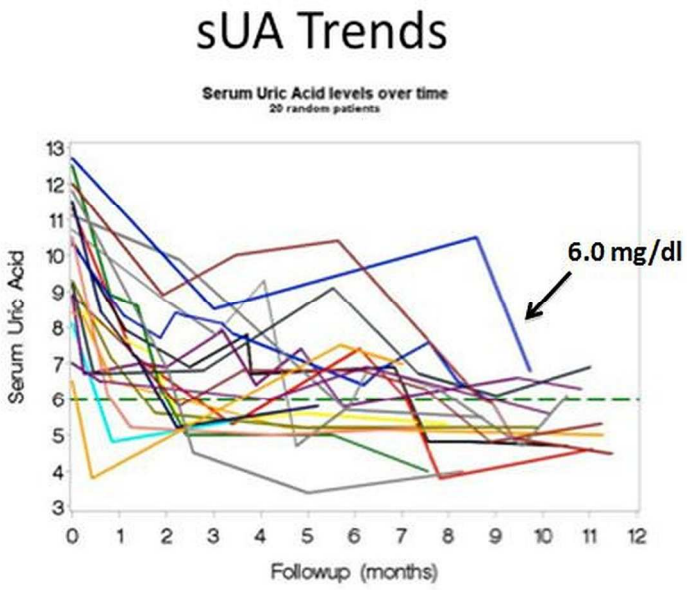

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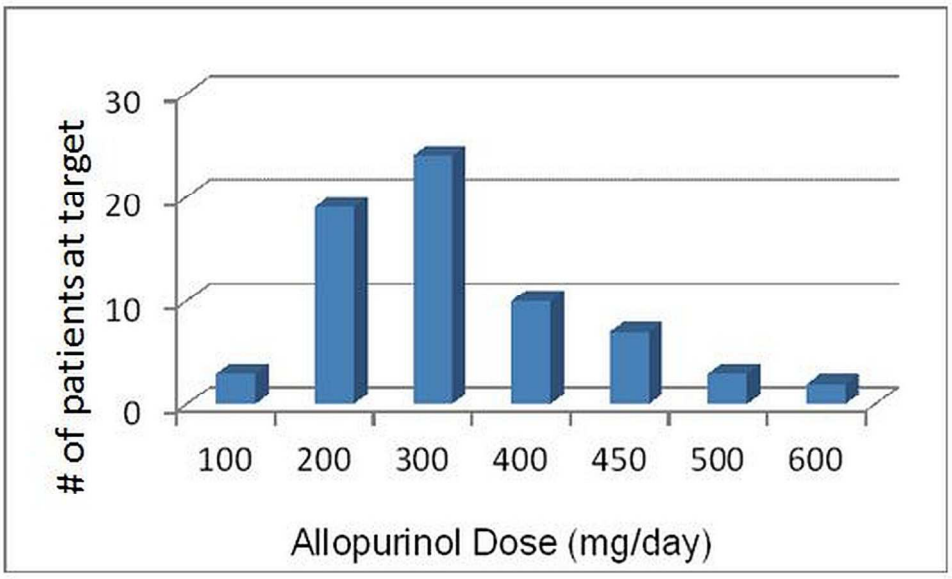

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