4-14-2017

Treatment Considerations of Gout in the Patient With Chronic Kidney Disease in the Primary Care Setting

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Degree Master of Science

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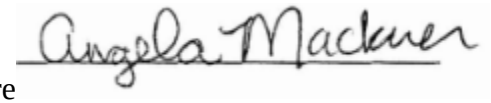
Signature 

Date 4/13/17

Abstract

Gout is a disease of recurrent, painful inflammatory episodes. While it is rarely life threatening, it can lead to disability after repeated attacks and resulting joint damage, therefore adequate control of acute inflammatory episodes and chronic hyperuricemia in the patient with gout is imperative. Patient M presented to the primary care clinic with a classic case of podagra. He, much like the other approximately 4% of the population that presents to their primary care provider with gout each year in the United States, had multiple secondary risk factors and comorbidities seen in the development of gout (Shmerling, 2012).

Comorbidities are frequently seen in the patient with gout, and the American Academy of Rheumatology recommends screening for comorbidities this patient population (Khanna et al., 2012). Patient M had a history of type 2 diabetes, hypertension, dyslipidemia, nephrolithiasis, obesity, recent alcohol use, high intake of purine rich foods, and thiazide diuretic use. These are all risk factors or comorbidities seen in patients with gout. At his office visit, his creatinine and glomerular filtration rate (GFR) were within normal limits; however, his multiple co-morbidities place him at a higher risk for chronic kidney disease, which could potentially complicate his treatment options in the future. Dalbeth, Merriman, and Stamp (2016) cited that 71% of patients with gout also have chronic kidney disease of stage 2 or greater. Also, hyperuricemia itself has been documented in epidemiological studies to be associated with the onset of new chronic kidney disease (Abdellatif & Elkhalili, 2014).

The current cornerstone of gout therapy is multi-faceted. In addition to lifestyle modification, anti-inflammatory treatment during the acute periods of inflammation with low dose colchicine, non-steroidal anti-inflammatory drugs (NSAIDs), or corticosteroids is

recommended. NSAIDs are often contraindicated in patients with any degree of chronic kidney disease due to risk of acute kidney injury. NSAID use also puts patients at risk of possible gastrointestinal complications. Colchicine has significantly reduced clearance in patients with chronic kidney disease and is associated with multiple serious drug-drug interactions, including simvastatin, and CYP3A4 and P-glycoprotein inhibitors (Abdellatif & Elkhalili, 2014; Stamp, 2014). Anti-inflammatory agents are recommended prophylactically for at least 6 months following initiation of urate-lowering agents, therefore the provider must carefully select an agent that the patient with impaired renal function will tolerate (Khanna et al., 2012).

In addition to treatment in acute flares of gout, urate-lowering therapies are utilized for treatment in patients with two or more episodes of gouty arthritis per year and chronic hyperuricemia (Dalbeth et al., 2016). Uric acid kidney stones and the diagnosis of chronic kidney disease of stage 2 or greater is considered an indication for treatment with urate-lowering therapy by the American College of Rheumatology guidelines (Khanna et al., 2012). While Patient M had a history of nephrolithiasis, the type of stone was unknown. Urate-lowering therapies include the use of allopurinol and febuxostat, which are both classified as xanthine oxidase inhibitors, probenecid, which promotes normalizing of serum urate through urinary excretion, and uricolytics, such as pegloticase (Dalbeth et al., 2016; Shmerling, 2012).

Urate-lowering therapy for the treatment of gout requires dose adjustment or consideration of use in the patient with chronic kidney disease. For example, Stamp, et al. (2012), noted that in the patient with renal impairment, doses of allopurinol greater than or equal to 300 milligrams per day is associated with allopurinol hypersensitivity syndrome (AHS). The American College of Rheumatology guidelines for gout management suggest beginning urate-lowering therapy with lower doses of allopurinol, however the lower doses are often ineffective

at reaching serum urate goals. And, probenecid is contraindicated in patients with a creatinine clearance of <50ml/min (Khanna et al., 2012).

With gout and chronic kidney disease being of such common prevalence in the United States, the fact that one condition exacerbates the other, and the need for modification of typical medication management of gout in the patient with chronic kidney disease, the purpose of this report is to review literature that discusses changes to the medication regimen for treating patients in primary care with acute gouty arthritis and chronic kidney disease.

Case Report

Patient M, a 46 year-old Caucasian male with a history significant for obesity, hypertension, type 2 diabetes mellitus, hypercholesterolemia, and nephrolithiasis presented to the primary care clinic with complaints of pain and swelling in his right great toe. His discomfort had started acutely the morning of his presentation. He described it as a continuous, throbbing-type pain. It did not radiate. He rated his pain a 6 on a 0-10 scale. He denied any over-the-counter attempts at managing his pain at home. He denied injury to the area. He also denied fever, chills, chest pain, shortness of breath, claudication, and history of neuropathy and ingrown toenail. As a diabetic, he did not report seeing podiatry routinely; however, he stated that his last visit to his primary care provider was two months ago, and since that time there has been no change in his condition, except his great toe pain. He checks his blood sugar occasionally at home and his results have been in the low 100s. He stated that yesterday he partook in a game of curling with a group of friends and after this he consumed approximately three alcoholic beverages in the form of beer. He also reports frequent consumption of sardines. His current medications included metformin, lisinopril, hydrochlorothiazide, aspirin, and a statin.

He was afebrile and his other vital signs were within normal limits. He was considered obese, with a body mass index (BMI) of 29. His physical exam revealed a 46 year-old Caucasian male sitting upright in the exam room. He was in no acute distress. He was alert and oriented to person, place, and time. He was felt to be a reliable historian. His lungs were clear throughout all fields and his heart tones were regular without skips, gallops, or rubs. Monofilament testing was within normal limits to bilateral feet. There were 2+ pedal pulses and 2+ posterior tibial pulses noted bilaterally. On inspection, his right first metatarsophalangeal joint was erythematous, warm, and slightly edematous. Tenderness was reported on light palpation. In general, skin to feet and ankles was intact and without laceration or abrasion. Toenails were in good condition.

After history taking and physical exam, the likely diagnosis was acute gouty arthritis. Differentials included soft tissue cellulitis, septic arthritis, and rheumatoid arthritis. Laboratory evaluation including basic metabolic panel, complete blood count, erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, and uric acid was obtained and revealed elevation of his uric acid at 10.9. Because of this, joint aspiration of the right first metatarsophalangeal joint was carried out, which revealed monosodium urate crystals, confirming the diagnosis of acute gouty arthritis. The patient was treated with oral non-steroidal anti-inflammatory agent, Naproxen. Dietary counseling was provided regarding reducing intake of high purine foods, including alcohol and sardines. Non-weight bearing to right foot and rest until resolution of acute attack. The patient was instructed to return to the clinic in one week for monitoring of his acute gouty arthritis and blood pressure management. This was his first episode of gout, therefore urate-lowering therapy was not considered.

Patient M presented to the clinic with a classic case of acute gouty arthritis. He had multiple risk factors for acquiring this condition including: male gender, hypertension, history of

kidney stones, intake of purine rich foods including sardines and alcohol, increased weight, and use of the medication hydrochlorothiazide for blood pressure management. The management of his condition was straightforward, as his laboratory evaluation was without abnormality with the exception of his uric acid. A potential confounder in the management of his gouty arthritis if it recurs in the future could possibly include chronic kidney disease, a condition for which he already possesses risk factors for at the age of 46; including hyperuricemia, hypertension, and diabetes. Multiple considerations are taken when prescribing treatment for gout in the patient with chronic kidney disease. As stated earlier, the pathophysiology of one disease process contributes to the development of the other.

Literature Review

While there are multiple medications available for both the acute inflammatory periods and chronic urate-lowering therapy in gout, providers must be aware of potential complications of treatments and safe alternatives for patients with chronic kidney disease. This literature review will address treatment options in the acute inflammatory period and chronic urate-lowering therapy in the patient with chronic kidney disease in primary care. Presently, there are new inhibitors of the pro-inflammatory cytokine interleukin-1B that have been studied in acute gouty arthritis; however, they were excluded from this review as they present cost barriers and are not commonly utilized in the primary care setting (Abdellatif & Elkhalili, 2014).

Acute Inflammatory Management in Chronic Kidney Disease

The most effective management strategy in the acute inflammatory period of gouty arthritis is to begin anti-inflammatory treatment at the earliest sign of an acute flare (Gaffo & Saag, 2008). NSAIDs, such as naproxen and indomethacin, and colchicine are generally

contraindicated in chronic kidney disease. While corticosteroids can have detrimental adverse effects in long-term use, in the primary care setting, corticosteroids may be the preferred treatment option for acute gouty arthritis in the patient with chronic kidney disease.

Rainer et al. (2016) performed a double-blind, randomized trial comparing oral prednisolone to indomethacin and their effectiveness in the treatment of acute gout. Each of the medications was used in combination with acetaminophen. In their study, patients, mostly male with a mean age of 65 years, who presented to the emergency department in Hong Kong with acute gouty arthritis were randomized to receive either indomethacin 50mg three times daily for two days and then 25 mg three times daily for three days, or oral prednisolone 30 mg per day for five days (Rainer et al., 2016). Renal insufficiency was reported by 35% of the patients (Rainer et al., 2016). They evaluated the effectiveness of each medication by monitoring joint pain at rest and with activity two hours after receiving the medication, and at day fourteen following treatment. Adverse events (dizziness, sleepiness, nausea, vomiting, abdominal pain, indigestion, rash, dry mouth, and any other symptom the patient reported) were also monitored. Fewer patients in the prednisolone group had adverse events in the first two hours. The groups did not differ in adverse events at day fourteen, and the groups did not differ for change in pain at day 14 (Rainer et al., 2016). There were no serious adverse events in either group. This showed that prednisolone was as effective as indomethacin in these patients. Limitations included the comparison of just indomethacin as an NSAID compared to the prednisolone, and the fact that diagnosis was based on clinical assessment, not necessarily on joint aspirate. Due to the fact that both medications were used in combination with acetaminophen as needed, one cannot conclude that prednisolone alone was efficacious in the management of acute gouty arthritis.

While Rainer et al. used indomethacin in comparison to prednisolone, Janssens, Janssen, van de Lisdonk, van Riel, and van Weel (2008), performed a double-blind, randomized equivalence trial of naproxen versus prednisolone in the treatment of gouty arthritis in the primary care clinic. Their study included 59 patients randomized to receive prednisolone 35 mg once daily for five days, and 59 patients randomized to receive naproxen 500mg twice daily for five days (Janssens et al., 2008). 89% of the subjects were male and their average age was 57 years old. Some eligible patients in this trial were excluded due to possible risks, such as gastrointestinal bleeding and pre-existing renal disease, if treated with NSAIDs. They compared pain ratings of each group after 90 hours of treatment and found equivalent reduction in pain scores between the two groups (Janssens et al., 2008). The adverse effects (gastric or abdominal pain, itch or dizziness, dyspnea or palpitations, or other adverse effects) described by 66% of the patients taking prednisolone and 63% of the patients taking Naproxen had all resolved by three weeks after the study (Janssens et al., 2008). Although this study was much smaller compared to the comparison of indomethacin and prednisolone, the subjects included here had confirmed monosodium urate crystals on joint aspiration. It is possible that Rainer et al. were treating patients that were unaffected by gout and were suffering from another condition, such as reactive arthritis, rheumatoid arthritis, or pseudogout. This a potential confounder in their findings.

Another study comparing the analgesic efficacy, anti-inflammatory effect, and tolerability of the corticosteroid, prednisolone, to indomethacin, and etoricoxib, a selective cyclooxygenase (COX)-2 inhibitor, in acute gout was completed by Xu, Liu, Guan, and Xue in 2016. This study was completed in China, was open label, and was randomized. Xu, et al. (2016), analyzed a total of 113 patients, mostly men with a mean age of 44 years old, diagnosed with acute gouty arthritis based on clinical criteria. The patients were given either 35 mg of

prednisolone daily, etoricoxib 120mg daily, or indomethacin 50 mg three times daily. Adverse effects over four days were recorded. Adverse effects included gastric or abdominal pain, dizziness, edema, fatigue or drowsiness, and dry mouth. The three medications were similar in their ability to reduce pain, while prednisolone may have been slightly more effective in reducing swelling (Xu, et al., 2016). Indomethacin was associated with more adverse effects compared to etoricoxib, but none of the adverse effects were serious (Xu, et al., 2016). Limitations of this study included its small sample sizes and lack of absolute confirmatory aspirate revealing monosodium urate crystals. Compared to Rainer, et al. (2016), this study did not utilize prednisolone in combination with acetaminophen, perhaps leading one to be able to draw the conclusion that prednisolone alone is effective in the management of acute gouty arthritis.

Wechalekar, et al. (2014) performed a systematic review comparing acute gout management therapies and their effectiveness of pain management and adverse events. This review included a Cochrane Review. Five studies looked at glucocorticoids, 21 studies looked at NSAIDs, two studies reviewed colchicine, and one study reviewed the interleukin inhibitor, canakinumab (Wechalekar, et al., 2014). Through their review, Wechalekar, et al. (2014) were able to conclude that systemic glucocorticoids appeared safer than NSAIDs and colchicine, and that systemic glucocorticoids were just as effective at management. Systematic reviews are generally regarded as providing high quality evidence. While parts of this systematic review are not applicable to this literature review, this provides evidence again for the safety and efficacy of short-term glucocorticoid use in acute gouty arthritis.

Management of Chronic Hyperuricemia in Chronic Kidney Disease

Beyond the acute inflammatory phase of gout, many patients require urate-lowering prophylactic therapy to prevent recurrent attacks and resulting disability from joint damage. Allopurinol is a frequently used urate-lowering therapy that in the past, was dosed based on the Hande criteria, utilizing the patient's creatinine clearance (Stamp, et al., 2011). Stamp, et al. (2011) enrolled 90 patients who had been on allopurinol for at least one month, and incrementally increased their allopurinol dose by 50-100mg each month if their serum urate concentration was greater than or equal to 6mg/dl, until their serum urate concentration was less than 6mg/dl. 87.9% of the patients enrolled were male and their average age was 58.7 years old (Stamp, et al., 2011). The patients had multiple co-morbidities. 45 of the patients enrolled had serum urate concentrations greater than or equal to 6mg/dl while on the allopurinol dose that was based on their creatinine clearance, and therefore underwent incremental dose adjustments of their allopurinol (Stamp, et al., 2011). After 12 months of dose increases, the mean dose of allopurinol was 359.7 mg/day, and the patients were able to achieve a serum urate level less than 6 mg/dl without adverse reaction (Stamp, et al., 2011). This study shows that when using allopurinol in patients with renal impairment, one can safely increase allopurinol dosing with careful monitoring in order to achieve serum urate levels less than 6mg/dl. The likely benefit of having serum urate levels at below saturation far outweigh the risk of developing the AHS in the patient with renal impairment. This study was small, so larger studies would be indicated, but its importance is great when considering the cost of allopurinol versus other urate-lowering therapies.

Thurston, Phillips, and Bourg (2013) also had interest in studying the safety and efficacy of allopurinol in the patient with chronic kidney disease. They performed a literature review to

determine if a renally-dosed regimen of allopurinol had been consistently studied in the literature. They found that randomized-controlled trials of the use of allopurinol in gout in patients with chronic kidney disease is lacking, and that the studies that have been completed have not demonstrated consistency regarding the safety and efficacy of allopurinol (Thurston et al., 2013). The studies reviewed also lacked consistency in their definition of chronic kidney disease (Thurston et al., 2013). From their review they drew the conclusion that definitive research is needed, and that providers should be aware of the need to educate patients with chronic kidney disease who are placed on allopurinol about the possibility of and signs and symptoms of AHS (Thurston, et al., 2013).

Research of allopurinol in gout management in the setting of chronic kidney disease has not been definitive. Febuxostat, a non-purine analogue xanthine-oxidase inhibitor, which is metabolized by both the kidneys and the liver, has been studied for its ability to lower urate levels effectively in patients with renal impairment (Tsuruta et al., 2014). Tsuruta et al. (2014), examined a cohort of 73 hyperuricemic patients who had an estimated glomerular filtration rate (eGFR) below 45ml/min and were already on urate-lowering therapy with allopurinol for changes in urate levels and eGFR with therapy of febuxostat versus continued allopurinol therapy after one year. 51 patients were prescribed febuxostat in place of allopurinol, and 22 patients were continued on allopurinol. After one year of treatment, febuxostat patients had lower uric acid levels, while the allopurinol cohort's uric acid levels actually increased.

While this study looked promising for use of febuxostat, there were significant limitations. The sample of patients studied was small. The dosing of febuxostat was not standardized, as patients were treated with both 10 mg and 20 mg doses. Also, the allopurinol group was likely under treated, as there was no up titration of allopurinol based on patient

tolerance. The allopurinol cohort was treated with either 50 mg, 100 mg, or 200 mg throughout the study. The patients in this study had an eGFR <45 ml/min, so one may hypothesize that the 10 mg or 20 mg dose of febuxostat would be safe to use in patients with better kidney function. Something that also must be considered is the cost effectiveness of feboxostat versus allopurinol.

Saag et al. (2016) also examined febuoxstat in renal impairment. They examined serum urate reduction and renal function by performing a randomized, double-blind, placebo-controlled study comparing 96 patients with gout, serum uric acid levels greater than or equal to 7 mg/dl, and moderate to severe renal impairment (eGFR of 15-50 ml/minute) (Saag et al., 2016). They randomized their patients at a 1:1:1 to receive 30mg febuxostat twice daily, 40/80 mg febuxostat once daily, or placebo (Saag et al., 2016). A total of 57 patients completed the study and the highest percentage of patients that withdrew from the study due to an adverse event were from the placebo group (Saag et al., 2016). After 12 months, serum creatinine and eGFR were not significantly changed in all groups; however, in the febuxostat groups, there was significantly better reduction in serum urate levels to a serum urate level of less than 6 mg/dl. A possible confounder in this study was the fact that there was a heavy proportion (53%) of patients in the placebo group with severe renal impairment.

Sakai et al. (2014) compared febuxostat and allopurinol in the Japanese population with eGFR less than 60ml/minute, who had failed to achieve serum uric acid concentration of less than 6 while on allopurinol, and who had been on febuxostat for six months or longer. They used a retrospective observational exploratory study (Sakai et al., 2014). Sakai et al. (2014) reviewed medical records of 60 patients and compared serum uric acid levels 6 months before and 6 months after switching to febuxostat. The average dose of allopurinol prior to febuxostat use was 71.3 mg/day, and febuxostat was dosed between 10-40 mg (Sakai et al., 2014). After 6 months of

febuxostat treatment, mean serum uric acid concentrations decreased from 8.4 mg/dl to 6.2 mg/dl, and there was an increase in eGFR with febuxostat treatment (Sakai et al., 2014). In their review, Sakai et al. (2014) repeatedly mentioned that prior to the placement on febuxostat, the patients on allopurinol had a, "slow but steady decline in eGFR" in the 6 months prior to the switch. While this may be true, one must question the aggressiveness and up-titration of allopurinol dosing (based on patient tolerance) in order to reduce serum urate in the patient population. This sample was again, small. The retrospective observational study lacks strength of quality of evidence, so further study in a larger patient population is needed.

The final study reviewed was completed by Schumacher et al. (2008) and was a randomized, double-blind trial that compared urate-lowering efficacy of febuxostat, allopurinol, and placebo in 1,072 subjects with hyperuricemia (serum urate greater than 8) and gout. The study included a small subset of patients with impaired renal function, with serum creatinine ranging from greater than 1.5 mg/dl to less than or equal to 2 mg/dl. In the group with impaired renal function, 25 subjects were treated with varying doses of febuxostat (80mg, 120mg, or 240mg daily) and 10 subjects were treated with allopurinol 100mg daily (Schumacher et al., 2008). The study took place over 28 weeks and the effectiveness of each treatment was based on a monthly serum urate level during each of the last three months of the trial (Schumacher et al., 2008). 12 of the 25 subjects with impaired renal function treated with febuxostat reached the goal serum urate level of less than 6, while 0 of the 10 subjects treated with 100mg of allopurinol reached the goal serum urate level (Schumacher et al., 2008). While this study was a randomized-controlled trial, it contained a very small subset of patients that had impaired renal function. And, like the other studies comparing allopurinol effectiveness versus febuxostat effectiveness in the patient with chronic kidney disease, the allopurinol was likely under dosed.

There was no attempt at up titration, which places allopurinol at somewhat of an unfair advantage.

Learning Points

Much thought, time, effort, and study was placed into this work, and with this comes an expansion of knowledge about the general condition of gout, the risk factors for the condition, and different options for treatment. Currently there are multiple studies in the literature about hyperuricemia, gout, and the relationship to chronic diseases, specifically chronic kidney disease and cardiovascular disease. It seems that uric acid may be on the horizon of being a laboratory value that is routinely monitored in primary care. As gout and chronic kidney disease are frequently encountered in primary care, it seemed valuable to evaluate their management.

- The management of gout is multi-faceted, and this concept was applied in Patient M's care. He received education about lifestyle management. Medication was prescribed for the acute inflammatory episode, and consideration for future treatment options was given.
- Short-term, or "burst" corticosteroid therapy, specifically with prednisolone, as reviewed above, appears safe for use in the patient with acute gouty arthritis and chronic kidney disease. Corticosteroid use while initiating urate-lowering therapy could also be used in the patient with renal impairment (recommended to continue anti-inflammatory treatment for 6 months).
- Urate-lowering therapy is considered in the patient with stage 2-5 chronic kidney disease and in patients with hyperuricemia and two or more episodes of acute gouty arthritis per year. This literature review focused on the use of allopurinol and febuxostat as options

for patients with chronic kidney disease. The provider and patient must be willing to work together with up-titration to achieve serum urate goals of 6 or less.

- An up titration of allopurinol could first be considered if cost of care is an issue before moving to febuxostat for urate-lowering therapy.
- Febuxostat has been proven effective for serum urate-lowering in the patient with chronic kidney disease. Some studies have included patients with severe renal impairment, which likely would be addressed in nephrology rather than primary care, but is still useful for the primary care provider to have knowledge of.

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