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Management of Gout and Hyperuricemia in CKD

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Abstract

Hyperuricemia and gout, the clinical manifestation of monosodium urate crystal deposition, are common in patients with chronic kidney disease (CKD). While the presence of CKD poses additional challenges in gout management, effective urate-lowering is possible for most patients with CKD. Initial doses of urate-lowering therapy are lower than in the non-CKD population, while incremental dose escalation is guided by regular monitoring of serum urate to reach the target of less than 6 mg/dL (or less than 5 mg/dL for patients with tophi). Management of gout flares with presently available agents can be more challenging due to potential nephrotoxicity and/or contraindications in the setting of other common comorbidities. At present, asymptomatic hyperuricemia is not an indication for urate-lowering therapy, though emerging data may support a potential renoprotective effect.

INDEX WORDS

Hyperuricemia; gout; chronic kidney disease; urate-lowering therapy; allopurinol; febuxostat; uricosurics; uricase; colchicine; nonsteroidal anti-inflammatory drugs; glucocorticoids; management; review.; Supplemented with renal failure; hemodialysis; kidney transplant; chronic gout; acute gout; gout flare; therapy; treatment

CASE PRESENTATION

A 58-year old man with long-standing non-tophaceous gout presents to the emergency room with incapacitating pain due to arthritis in the left knee and right first metatarsophalangeal (MTP) joint. He has chronic kidney disease (CKD), currently stage 3b (estimated glomerular filtration rate (eGFR) of 32 mL/min). His most recent serum urate (SUA) level is 7.9 mg/dL.

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He is currently taking allopurinol 100 mg/day, a dose that was based on his creatinine clearance (CrCl). He also has hypertension, dyslipidemia, and congestive heart failure. He avoids non-steroidal anti-inflammatory drugs (NSAIDs) and limits his colchicine prophylactic dose to one tablet every other day due to his kidney disease. He has also been told by his cardiologist to avoid prednisone due to possible fluid overload with resultant decompensation of his congestive heart failure (CHF). This is his third visit to the emergency room within the last year due to gout-related pain.

INTRODUCTION

Gout, the clinical manifestation of crystalline monosodium urate (MSU) deposition, is the most common inflammatory arthritis in adults, especially in men, with increasing prevalence worldwide, ranging from 0.1 to 10% and estimated to be 3.9% in the US.[1,2] Hyperuricemia, which is biochemically defined as SUA ≥6.8 mg/dL based on the limit of urate solubility, is even more common. Using population level sex-specific SUA distributions to define hyperuricemia, a US study reported a prevalence of 21.2% among men (SUA >7.0 mg/dL) and 21.6% among women (SUA >5.7 mg/dL).[2]

As two-thirds of human urate excretion occurs through the kidneys, with the remaining one-third occurring through the gastrointestinal tract, decreased kidney function is associated with hyperuricemia. On the other hand, several large epidemiologic studies and small trials suggest that hyperuricemia may potentially be associated with the development and progression of hypertension and CKD.[3] Regardless of which is cause or consequence, the association of CKD with gout and hyperuricemia is common.[4,5] Approximately 20% of adults with gout have CKD stage ≥3 compared with 5% of individuals without gout; 15% of adults with hyperuricemia have CKD stage ≥3 compared with 3% of individuals without hyperuricemia.[6] The age-standardized prevalence of gout and hyperuricemia increases as kidney function declines, with 24% of adults with eGFR <60 mL/min having gout compared with 2.9% of adults with eGFR ≥ 90 mL/min.[5]

Clinicians are frequently confronted, therefore, with managing gout in the setting of kidney disease. The management of gout flares can be challenging because of cautions or contraindications in those with diminished kidney function as well as other common comorbidities that occur frequently in CKD. Among adults with CKD stage 3, 87.8% have hypertension, 16.9% have diabetes, 22.9% have ischemic heart disease, and 3.5% have CHF.[7] Similarly, patients with gout, irrespective of kidney disease, have high prevalence of these conditions.[6] These comorbidities impact therapeutic decision making, particularly for gout flare management since the agents available have precautions and/or contraindications in these settings. On the other hand, there is often unnecessary excessive concern regarding urate-lowering therapy (ULT) in the context of CKD, frequently leading to inadequate management of gout.

CLINICAL CONTEXT

The most typical presentation of gout is the acute onset of a monoarthritis, generally affecting the lower limbs (classically the 1st MTP joint), lasting 7–14 days without therapy,

followed by an asymptomatic period of varying duration.[8] Without treatment, flares tend to recur progressively more frequently, last for longer periods and can become more resistant to treatment for some. In later stages, a chronic inflammatory arthritis can occur with persistent symptoms; often tophi develop with longer duration of disease, although occasionally tophi can be the initial clinical manifestation of gout.[9] In women, the first presentation of gout generally occurs after menopause because of the uricosuric effects of estrogen.[10] While mono- or oligoarthritis of a lower limb is a common gout flare presentation, other patterns are not infrequent, such as upper limb involvement and polyarticular flares.[11] Patients with CKD are anecdotally thought to have more variable presentations of their gout flares, including higher frequency of polyarticular flares. These presentations are also more common among women and elderly individuals, and often are associated with diuretic use and CKD.[12–14] Thus, clinicians must remember to consider gout flare in their differential diagnosis of acute joint complaints in a patient with kidney disease, even if the pattern of joint involvement is not “classic”.

The diagnosis of gout is confirmed by the identification of MSU crystals under polarizing microscopy in synovial fluid aspirated from a joint or bursa or in material aspirated from a tophus. This gold-standard confirmation is especially important for patients with CKD, among whom the prevalence of other conditions that mimic gout is also common, such as calcium pyrophosphate (CPP) deposition disease (formerly known as “pseudogout”, and now labelled acute CPP crystal arthritis), for which the diagnosis is also confirmed by synovial fluid analysis.[15]

In the absence of a crystal-proven diagnosis, other elements of the history and physical exam can be helpful in supporting a diagnosis of gout. While not intended for use in making diagnoses, the 2015 American College of Rheumatology (ACR) - European League Against Rheumatism classification criteria for gout highlight some of the key factors to consider when evaluating an individual for the possibility of gout.[16,17] Classification criteria are intended for use in research to identify individuals for enrollment into clinical studies, and therefore do not necessarily cover the full spectrum of the disease.

MANAGEMENT OF GOUT IN CKD

The management of gout follows the same four principles regardless of the presence of CKD: 1) lower SUA (i.e., manage the hyperuricemia); 2) provide prophylaxis while initiating ULT; 3) treat gout flares; and 4) optimize dietary and lifestyle factors as appropriate. Over a prolonged period of time with adequate management of hyperuricemia, defined as maintenance of a SUA level <6 mg/dL or <5 mg/dL for those with tophaceous gout, gout flares will diminish in frequency and severity, with eventual cessation of flares, and tophi can be prevented and/or resolve.

Management of Hyperuricemia

Hyperuricemia is a necessary, though not sufficient, cause of gout since there are many more individuals with hyperuricemia than with clinically evident gout. Nonetheless, the mainstay and primary focus of gout therapy is to lower elevated SUA to achieve the clinical outcomes

that matter to patients: cessation and prevention of flares, resolution and prevention of tophi, and control of inflammatory arthritis for those with chronic gouty arthritis.

In 2012, the ACR published guidelines for the management of gout.[18,19] New in these guidelines was the recommendation to initiate ULT with the first flare of gout in patients with CKD stage 2 and worse.[18] The rationale for this new ULT indication is that these patients often have limited options for gout flare management. By initiating ULT earlier, the aim is to avoid the need to treat subsequent gout flares with potentially nephrotoxic or contraindicated agents. For patients with normal eGFR, indications for ULT continue to include recurrent gout flares (≥2 per year), tophi, and nephrolithiasis. In addition imaging evidence of tophi is a new indication for ULT.

In line with other treatment guidelines, the ACR guidelines noted insufficient evidence to address management of asymptomatic hyperuricemia.[18,20–22] As reviewed below, there are emerging data regarding potential benefit of ULT in CKD beyond the context of gout that points to the need for large trials to definitively address this issue.

Non-pharmacological approaches can be recommended to all gout patients as adjunctive measures; these include weight loss and avoiding excess intake of purine-rich foods, alcoholic beverages and fructose-rich beverages. Total prohibition of purine intake is not recommended since the impact on SUA is limited (reduction of approximately 1 mg/dL) and this represents a great burden for the patient; thus lifestyle approaches should be considered adjunctive and should not replace pharmacologic treatment.[23] Further, since the primary determinant of hyperuricemia in most patients is related to kidney clearance of uric acid, either reflecting inherited kidney transport factors and/or low eGFR, blaming the patient for their gout is counterproductive and contributes to poor management of gout as patients are reluctant to discuss their condition with health care providers.[24,25]

Pharmacological therapy for lowering SUA includes uricosuric agents that address the most common cause of hyperuricemia, kidney urate underexcretion, xanthine oxidase inhibitors that prevent purine metabolites from being converted to UA, and uricase therapy that oxidizes UA through an enzymatic reaction that is no longer present in humans to the highly soluble end-product, allantoin (Table 1). At lower GFR levels, uricosuric agents may not be efficacious; accordingly agents with other mechanisms of action need to be used. While dialysis in principle is uricosuric and is often accompanied by a reduction in gout flares despite persistent hyperuricemia, dialysis patients may still require ULT to achieve the SUA target and tophus resolution.[26,27] There are other mechanisms also being targeted, though none are advanced enough in their development for approval or clinical use.

Regardless of which ULT is chosen, general principles include: initiation of therapy concomitantly with prophylaxis; use of a low starting dose followed by regular monitoring of the SUA level with ongoing dose titration until the target is achieved; ULT should not be withdrawn or have its dose changed during gout flares; and SUA should continue to be monitored with additional dose adjustments as needed (Box 1). Optimally, ULT should be initiated when the patient is free of a gout flare, although the 2012 ACR gout treatment guidelines propose that ULT could be started during a gout flare as long as effective anti-

inflammatory therapy has been established. However, this approach has not been fully tested for potential negative consequences, such as prolonging a flare, and can add to a patient's confusion about which medication is being used for which purpose.[38,39]

Box 1

General approach to managing hyperuricemia in gout patients

Initiate anti-inflammatory prophylaxis concomitantly with or before starting urate-lowering therapy

Start urate-lowering therapy at a low dose and titrate dose to serum urate target

Check serum urate regularly

Aim for a serum urate target level of <6 mg/dL for most patients; consider <5 mg/dL for some, such as those with tophi

Maintain anti-inflammatory prophylaxis for at least 6 months, continuing until after both serum urate target achievement and resolution of clinical manifestations (last flare, tophus resorption)

Xanthine oxidase inhibitors (XOI)—Xanthine oxidase converts purine metabolites to UA. Thus, XOIs decrease the production of UA from endogenous and dietary purine sources and are considered first-line therapy, though uricosurics are an acceptable alternate first-line option.[18]

Allopurinol—Allopurinol, a purine base analogue available since the 1960's, is the most widely used ULT. Although it is effective, its appropriate use has been hampered by certain misconceptions. This is largely due to the decades-old proposed allopurinol dose adjustment according to CrCl to levels that should theoretically achieve the same serum level of oxypurinol, the active metabolite, as a 300 mg-dose of allopurinol would achieve in a patient with normal kidney function.[40] This algorithm was developed to theoretically mitigate against the risk for allopurinol hypersensitivity syndrome (AHS), which manifests as rash, eosinophilia, leukocytosis, fever, hepatitis and progressive kidney failure, with high mortality rates.[40] However, this strategy has never been proven to lower this risk in patients who tolerate low starting doses of allopurinol.[28] Further, with this dosing strategy, fewer than 50% of patients achieve the target SUA level.[18,41–44] Notably, the peak dose of allopurinol does not appear to be associated with AHS in patients with CKD; rather the risk of AHS is primarily related to the initial dose of allopurinol and whether the patient is a carrier of the variant HLA-B*5801 allele, and the risk is highest in the first 6 months of use.[45–51]

The dose of allopurinol can be safely increased beyond the CrCl-based dose in patients with kidney disease; allopurinol can be used in patients receiving hemodialysis or peritoneal dialysis who still require ULT, as detailed in Table 1.[45,52–55] For all patients initiating allopurinol, the starting dose should be low, specifically 50 mg/day for patients with CKD stage 4 or 5, and no more than 100 mg/day in all others.[18] Initiating ULT at a low dose aims

to reduce the risk of gout flare and of AHS or other allergic reactions. The daily dose should then be up-titrated by 50 to 100 mg every 2–5 weeks as needed to achieve the SUA target.[18]

Febuxostat—Febuxostat is a non-purine selective XOI that was FDA-approved in 2009. Trials assessing febuxostat's efficacy compared it with a fixed dose of allopurinol of 300 mg/day, or 200mg/day in those with some degree of kidney disease.[56–59] Since this dose of allopurinol is not sufficient to adequately achieve the SUA target for a majority of patients, it is not clear from these trials how superior febuxostat is in comparison with appropriately titrated allopurinol; a randomized controlled trial is currently underway to assess this. Febuxostat can be used in patients with eGFR ≥30 mL/min without dose adjustment. However, the data on efficacy and safety of febuxostat in CKD stages ≥3, including kidney replacement therapy, are limited. In the CONFIRMS trial, which randomized 2269 participants, only 18% had an estimated CrCl below 60 mL/min, while one of the largest trials of XOIs to date in people with CKD stage 3 and 4 only randomized 96 participants.[59,60] Most other trials included only subjects with CKD stage 2 or better. There are only some case reports, small clinical trials, and observational studies on use of febuxostat in patients on dialysis and/or with kidney transplant.[30–34,61,62]

Regarding side effects, the frequency of mild skin reactions was similar to those in allopurinol treatment arms in these trials, at ~2–5%.[56,57,59] Some severe cases of adverse cutaneous reactions have been reported, including drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, Stevens-Johnson syndrome and toxic epidermal necrolysis, particularly in patients with history of cutaneous adverse reactions to allopurinol and in patients with CKD, leading to a warning by the European Medicines Agency (EMA) and Health Canada regarding this issue.[63–67] No association between HLA-B*5801 allele status and these reactions has been reported to date. There was a potential cardiovascular safety signal in the initial febuxostat trials program, with additional trials required prior to approval.[68] In the postmarketing period, there have been some reported cases of heart failure leading Health Canada to request the manufacturer to include a warning for the risk of heart failure in patients with cardiovascular disease and/or other risk factors in the Canadian label.[69] Studies comparing the safety of febuxostat and allopurinol are currently underway.[70,71]

The cost-effectiveness of febuxostat has been evaluated in comparison with allopurinol. However, interpretation of these studies is challenging as some were sponsored by the manufacturer of febuxostat and most used suboptimal doses of allopurinol as the comparator arm.[72–75] The ACR guidelines does not distinguish between the two XOI since cost was not considered; allopurinol may therefore be a reasonable initial option for most patients.[76]

Uricosurics—Uricosuric agents act through transporter proteins involved in kidney urate reabsorption and/or secretion, such as UA transporter 1 (URAT1), glucose transporter 9 (GLUT9), organic anion transporter 1 (OAT1), OAT3, OAT4 and OAT10.

Uricosurics are underused, particularly in the US. This is partly related to the need for multiple tablets and twice daily dosing of probenecid, which, until recently, was the only uricosuric agent available in the US. Lesinurad, a uricosuric URAT-1 and OAT-4 inhibitor

approved by the FDA in 2015, must be co-prescribed with a XOI, because, in randomized trials, lesinurad monotherapy was associated with acute kidney failure more commonly than the comparator arms; thus an indication for monotherapy was not pursued. Creatinine rises noted during these trials were generally reversible. Benzbromarone is a more potent uricosuric drug but is not FDA-approved in the US and unavailable in some European countries due to concerns regarding hepatotoxicity.[77]

Uricosurics must be avoided in patients with prior nephrolithiasis and are contraindicated in the presence of uricosuria higher than 700–800 mg/24 hours. Patients on a uricosuric agent must assure adequate fluid intake due to risk of nephrolithiasis. Because uricosurics lose efficacy as kidney function declines, probenecid is not recommended for those with CrCl <30 mL/min, and lesinurad is not recommended for those with CrCl <45 mL/min.

While not developed as drugs that reduce urate, two commonly used drugs have uricosuric properties: losartan and fenofibrate. Losartan, an angiotensin receptor blocker, is commonly used in all stages of CKD. The safety of fenofibrate is uncertain in advanced kidney disease, particularly in combination with statins due to increased risk of rhabdomyolysis.

Uricase—Pegloticase is a pegylated recombinant porcine uricase, the enzyme responsible for converting UA to allantoin, which is more soluble than uric acid and therefore more easily eliminated. Its approved use is for gout that is refractory to oral ULT. Pegloticase is administered intravenously every two weeks, with the current label supporting 6 months of therapy, though longer term therapy has been successfully reported. Following completion of that regimen, patients are transitioned back to oral ULT. Because pegloticase is derived from porcine uricase and is pegylated, there is a risk for immunogenicity, with infusion reactions and anaphylaxis. The reported rate of hypersensitivity reactions was 26% and 44% for infusions every 2 weeks and monthly, respectively, in a 6-month study, and 44% in an open-label extension study (18% were severe reactions).[78,79] Anaphylaxis occurred in ~5% of subjects in the pivotal trials that led to approval.[78] Hypersensitivity reactions are highly correlated with rising SUA levels; thus SUA must be assessed prior to each infusion and therapy must be discontinued if SUA is >6mg/dL on two successive occasions. Pegloticase, which is administered with 250 mL of normal saline, can be used in advanced CKD, including in dialysis patients, without dose adjustment.[35] Reports of heart failure associated with pegloticase have prompted a label warning, advising exercising caution in patients who have congestive heart failure and monitoring patients closely following infusion.

Anti-Inflammatory Prophylaxis of Gout Flares

Colchicine and NSAIDs are considered first-line drugs for prophylaxis of gout flares, and less preferably low-dose glucocorticoids may also be considered when colchicine and NSAIDs are contraindicated (Table 2).[19] Current guidelines recommend prescribing prophylaxis for all patients initiating ULT and maintaining prophylaxis for as long as there is evidence of ongoing gout disease activity (i.e., flare or tophus) and/or the SUA target has not been achieved. In particular, prophylaxis should be continued for the greater of: at least six months, three months beyond reaching the SUA target for those without tophi, or six months

beyond reaching the SUA target for those in whom previously detected tophi have resolved.[19]

Management of Gout Flares

Gout flares, which are intensely painful episodes of self-limited arthritis, are usually the first clinical manifestation of gout. They are by far the most important manifestation of the disease for patients, and are the primary burden of this disease. Gout flares occur when MSU crystals activate the NLRP3 inflammasome, often in conjunction with a 2nd signal such as certain free fatty acids, leading to elaboration of interleukin(IL)-1β release.[81] The presence of MSU crystals alone is insufficient to cause gout flares as they can be detected in the synovial fluid of asymptomatic joints. Several factors have been identified that increase the risk of gout flares, including dietary factors (e.g., animal-derived purines, alcohol), hospitalizations (especially in the setting of surgery), and diuretics, among others. It is also well-recognized that initiation of ULT leads to an increase of gout flares in the short term. It is generally thought that fluctuations in SUA levels contribute to gout flares. Patients should be counseled regarding avoidance of pertinent dietary and lifestyle triggers.[19,82] Such a preventive strategy may be particularly important for patients with CKD who often have fewer therapeutic options for adequately treating gout flares.

Treatment options for gout flares in the US include colchicine, NSAIDs, glucocorticoids (oral, intra-articular, intramuscular, intravenous), and subcutaneous or intramuscular adrenocorticotropic hormone (ACTH), though there is limited evidence for this latter option. IL-1 antagonism with canakinumab is an approach approved by the EMA for management of gout flares, but not yet approved in the US.[83–85] Anakinra is occasionally used off-label in the US in patients for whom the other therapies cannot be used. Regardless of which therapeutic approach is used, the earlier the treatment is started, the faster the flare is brought under control. Local ice therapy can be used adjunctively.[86] A “medications-in-the-pocket” strategy should be encouraged for patients who understand their disease well to start treatment at the first signs of a flare; often immediate initiation of gout flare therapy can abort the attack entirely. General principles to consider for gout flare management are highlighted in Box 2 and specific considerations for patients with CKD are reviewed in Table 3 for each drug.

Box 2

General principles for gout flare management

Treatment options

- Colchicine
- Non-steroidal anti-inflammatory drugs
- Glucocorticoids (PO, IA, IM, IV)
- ACTH (SC, IM)
- Interleukin-1 inhibitors (off-label in the US)
- Ice

Time to start

- Immediately – “medications-in-the-pocket”. Note, colchicine is less effective if started >24 hours after a flare has started

Dose

- High dose, then taper

Duration

- 7–14 days (until flare resolves; otherwise a rebound flare can occur)

Urate-lowering therapy

- No interruption

PO: per os, oral; IA: intra-articular; IM: intramuscular; IV: intravenous; ACTH: adrenocorticotropic hormone; SC: subcutaneous.

Colchicine—Colchicine is most effective for managing gout flares when started within the first 36 hours based on its mechanism of action, pharmacokinetics and clinical data.[87] The recommended regimen for individuals with normal kidney function is 1.2 mg at the first sign of a gout flare followed by 0.6 mg one hour later based on fairly recent clinical trial data demonstrating similar efficacy and lower side effects with this strategy compared with a higher dose strategy.[19,88] Although colchicine was used off-label for decades to manage gout flares, this more recent trial led to FDA-approval of Colcrys for this new indication, with a resultant marked increase in price and difficulty in obtaining generic colchicine.[89] After this initial therapy, colchicine should be continued once or twice daily until resolution of the flare, or other gout flare therapy should be used.

For patients with CKD, colchicine must be used at lower doses with a number of caveats. Specifically, with CrCl ≥30 mL/min, dose adjustment is not required. Per the FDA approved package insert, for CrCl <30 mL/min, dose reduction is not required, but a treatment course should not be repeated within a two-week period. For patients treated with hemodialysis, the FDA insert states that only a single 0.6 mg dose should be used, and also not repeated within a two-week period; the same approach should be used for peritoneal dialysis patients. Importantly, if colchicine is already used for prophylaxis, it should not be used to treat a gout flare in CKD patients. The risk of neuromyotoxicity increases with declining kidney function and with concomitant use of many medications, including cyclosporine and lipid-lowering medications such as statins and fibrates (Box 3).

Box 3

Colchicine toxicity manifestations and risk factors

Toxicity Manifestations

- Neuromuscular toxicity

  May manifest as mildly as a tingling sensation or a subjective weakness or severely as overt peripheral neuropathy with axonal degeneration and

rhabdomyolysis; Common manifestations: proximal muscle weakness, elevated serum creatine kinase levels, neuropathy and/or myopathy on electromyography

- Blood dyscrasias

  Myelosuppression, aplastic anemia

- Gastrointestinal manifestations

  Anorexia, nausea, vomiting, bloating, diarrhea

- Pharyngeal pain
- Death

Risk Factors

- Decreased kidney function
- Hepatic dysfunction
- Elderly patients
- Statins[a]
- Fibrates
- High dose
- Concomitant use of P-glycoprotein or CYP3A4 inhibitors[b], such as:
  - Clarithromycin
  - Cyclosporine
  - Tacrolimus
  - Certain antifungals
  - Certain calcium channel blockers (verapamil, diltiazem)
  - Grapefruit juice

Special alert

Concomitant use of colchicine with P-glycoprotein or CYP3A4 inhibitors, especially clarithromycin, is contraindicated in patients with chronic kidney disease as it can result in death[90]

Non-steroidal anti-inflammatory drugs—There are no data to suggest that one NSAID is more efficacious than another. NSAIDs generally are avoided in individuals with CKD, particularly those with advanced CKD not receiving dialysis. Clinicians may consider

[a]Increased risk of myopathy is thought to be due to pharmacodynamics factors and/or competition for CYP450 or P-glycoprotein, and possible effects of impaired statin elimination via CYP450 and/or drug transporter (e.g., P-glycoprotein inhibition).[91] There is increased risk of myopathy/rhabdomyolysis with atorvastatin, fluvastatin, lovastatin, pravastatin and simvastatin.[92]

[b]Colchicine metabolism is performed by these systems, with colchicine being considered a major substrate of CYP3A4.

avoidance of NSAIDs in patients with concomitant diabetes mellitus even in the absence of obvious CKD given the high risk of kidney disease in such patients. Frequent use of NSAIDs for gout flare management can contribute to kidney disease. Cardiovascular risk and gastrointestinal bleeding risk need to be considered when NSAIDs are used, as for a non-dialysis population.

Glucocorticoids—When considering kidney safety, glucocorticoids may be the safest option for patients with CKD, remaining highly effective regardless of flare duration. A common regimen is to start with 0.5 mg/kg of body weight per day for the first few days, followed by progressive tapering.[9,19] Intra-articular glucocorticoid injection is preferable when only one or two joints are affected. Due to cross-reactivity with the mineralocorticoid receptor, there may be an increased risk of heart failure with many glucocorticoids, likely due to increased renal sodium avidity. Accordingly, for patients with concomitant CHF, dexamethasone may be the preferred formulation if the intra-articular route is not possible because it is considered to have the least mineralocorticoid potency.

Adrenocorticotropic hormone—Parenteral ACTH (subcutaneous or intramuscular) is considered an appropriate alternative to treat gout flares in patients who have restrictions to oral drugs, with no recommendation of dose adjustment in CKD, though its use lacks the support of rigorous clinical trial data.[19]

It is not uncommon for a patient with severe CKD to have limited improvement of their gout flare with the recommended lower doses of colchicine. Since NSAIDs are contraindicated, that leaves glucocorticoids as the primary option, though off-label use of the IL-1 antagonist, anakinra, is employed in some patients, particularly when glucocorticoids also cannot be used.

Additional special considerations for the management of gout in kidney transplant patients are shown in Box 4.

Box 4

Additional special considerations for the management of gout in kidney transplant patients.*

Immunosuppressant Drugs

- The use of xanthine oxidase inhibitors (allopurinol and febuxostat) is contraindicated with concomitant purine analogues, such as azathioprine and mercaptopurine, since this combination can result in higher and potentially toxic plasma concentrations of these drugs, leading to bone marrow suppression.
- Preferably avoid the hyperuricemic effects of cyclosporine.
- As such, mycophenolate mofetil should generally be the preferred immunosuppressant for gout patients with a kidney transplant.

*There are limited data regarding gout management in kidney transplant patients.

Urate-Lowering Therapy

- All available urate-lowering drugs may be considered, according to current level of kidney function.

Anti-Inflammatory Prophylaxis and/or Treatment of a Gout Flare

- NSAIDs should be used with caution and close monitoring of kidney function, considering their effects on kidney hemodynamics.
- Colchicine should be avoided in combination with cyclosporine and tacrolimus due to an increased risk of colchicine myotoxicity.

THE RELATION OF URIC ACID AND ULT TO KIDNEY OUTCOMES

CKD leads to hyperuricemia due to decreased urinary excretion of UA. Hyperuricemia also may induce kidney dysfunction and contribute to CKD progression through a number of potential mechanisms. It is possible that controlling hyperuricemia, especially if achieved early, may reduce kidney disease risk.

Mechanisms of hyperuricemia-induced kidney damage

Hyperuricemia may cause endothelial dysfunction, reflecting the effects of a reduction of nitric oxide bioavailability, the stimulation of oxidative stress, and the activation of the renin–angiotensin system.[3,93–95] Oxidative stress can stimulate smooth muscle cell proliferation of the afferent arterioles, thereby decreasing kidney perfusion. How much of these vascular effects are due to UA itself versus xanthine oxidase remains controversial.[93] Nonetheless, hyperuricemia induced in a rat model results in systemic hypertension, primary kidney arteriolopathy, and glomerular hypertension and hypertrophy, with resultant kidney hypoperfusion and eventual tubulointerstitial inflammation and fibrosis (Box 5).[96–100] When hyperuricemia was prevented or corrected to normouricemia early in the course of disease with allopurinol, febuxostat or benziodarone (an uricosuric), these manifestations were prevented.[96–101] In another rat model, allopurinol and benzbromarone limited the kidney damage caused by cyclosporine.[102] The effects of uricosurics (benziodarone, benzbromarone) in these experiments support the direct effects of UA rather than these effects being simply due to xanthine oxidase.

Box 5

Mechanisms by which hyperuricemia may contribute to kidney damage

Reduced nitric oxide bioavailability

Stimulation of oxidative stress

Activation of the renin–angiotensin system

Systemic and glomerular hypertension

Kidney vasculopathy

Tubulointerstitial inflammation and fibrosis

Hyperuricemia and kidney endpoints in observational studies

Though many observational studies have identified associations between hyperuricemia and CKD onset or progression, multiple others have not.[103–126] In a Japanese study of 48,177 subjects, SUA ≥6 mg/dL was an independent predictor of end-stage kidney disease in women,[104] and an increase in SUA over 10 years was an independent risk factor for eGFR decline.[115] Similarly, higher baseline SUA was also associated with kidney function decline in 16,186 patients with hyperuricemia enrolled in the Kaiser Permanente Southern California Health Plan.[116] Complementing these findings, hyperuricemia in healthy subjects free of kidney dysfunction at baseline in 3 large cohorts was associated with higher risk of developing kidney disease.[107,108] On the other hand, several observational studies have failed to identify a significant relation of SUA to CKD.[121–126] For example, in the Modification of Diet in Renal Disease Study, which followed 840 subjects with eGFR between 13 and 55 mL/min for up to 3.5 years, baseline SUA was not associated with CKD progression.[121] The Cardiovascular Health Study, a prospective community-based cohort of 4610 subjects followed for a mean of 6.6 years, found no association between hyperuricemia and incident CKD, although there was a modest association with CKD progression.[106]

Cohort Studies of ULT and Kidney Disease

Several observational studies have evaluated the effect of ULT on kidney function among subjects with normal kidney function and among patients with varying degrees of CKD and varying etiologies of kidney dysfunction (Table 4). While some are promising, definitive conclusions cannot be drawn from these observational studies of hyperuricemia and/or ULT on kidney effects, reflecting potential residual confounding and other biases including publication bias. Well-conducted clinical trials are needed for more valid insights to be drawn.

Randomized trial data of kidney effects of ULT

Only a few randomized clinical trials (Table 5) have assessed the effect of ULT, primarily allopurinol, on kidney outcomes. The febuxostat development program offered opportunity to gain insights into the effects of ULT on kidney function in the context of blinded randomized trials. However, while many trials were large, the numbers with CKD were small, subjects with advanced kidney disease (eGFR <30 mL/min/1.73m^2) were excluded, and kidney endpoints were not specifically reported as part of the main RCT publications, but rather as part of open-label extension studies which have the inherent validity issues of observational cohort studies.

In summary, the interpretation of the evidence to date regarding the role of UA in kidney disease and the potential renoprotective effect of urate-lowering is hampered by lack of high level evidence. Studies to date have largely evaluated allopurinol and febuxostat, which are both XOIs; thus, whether beneficial effects on kidney disease noted in some observational studies are truly related to lowering of urate versus inhibition of xanthine oxidase cannot be discerned. Evaluation of the effects of a uricosuric agent in the context of kidney endpoints

would provide further insights as to whether UA-lowering itself versus xanthine oxidase inhibition is the mechanism by which there appears to be promising renoprotective effects. Nonetheless, at the present time, treatment guidelines do not recommend treating asymptomatic hyperuricemia. Sufficiently powered, well-conducted, double-blinded, placebo-controlled randomized trials are needed to provide definitive direction into this important matter.

CASE REVIEW

For this patient, the first goal is to treat the current gout flare. Given his kidney disease and CHF, the optimal treatment would be intra-articular injection of the left knee and right 1st MTP joint. In lieu of that, a course of dexamethasone can be considered for its lower mineralocorticoid potency to minimize the risk of CHF exacerbation. Colchicine should be avoided since he already uses it for prophylaxis. Colchicine 0.6 mg every other day was continued for prophylaxis, and the allopurinol dose was kept stable until 2 weeks after the end of this gout flare, at which point his dose of allopurinol was increased to 200 mg daily, and further up-titrated based on regular monitoring of his SUA levels. He was also counseled regarding adjunctive lifestyle factors. At a dose of 450 mg/d, his SUA level was 5.6 mg/dL. Having achieved the target of <6mg/dL (since he has no tophi), he was maintained on this dose. After six months of his SUA remaining <6 mg/dL, colchicine was discontinued. After a year of therapy, he did not experience any further gout flares.

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Table 1

Urate-lowering agents with recommendations for urate-lowering management in patients with normal and reduced kidney function.

Urate-lowering agents	Doses	Recommendations for CKD 3–5	Recommendations for CKD 5D (dialysis)
Xanthine oxidase inhibitors (XOI)[a]			
Allopurinol	Starting: 50–100 mg daily; maximal approved: 800 mg/day (900 mg/day in the UK)	CrCl ≥30 mL/min: start with ≤100 mg/day[18]; CrCl <30 mL/min: start with 50 mg/day[18]	Intermittent HD: should be administered post-dialysis[28,29], start with 100 mg alternate days post-dialysis; daily HD: additional 50% of dose may be required post-dialysis; daily PD: start with 50 mg/day; all types of RRT: up-titrate dose with 50 mg-increments every 2–5 weeks, measure serum urate pre-dialysis
Febuxostat	Starting: 40 mg daily; maximal approved: 80 mg/day (120 mg in Europe)	Insufficient data for CrCl <30 mL/min	Despite some successful reports of dialysis patients using febuxostat up to 80 mg/day, this agent is not FDA-approved for use in dialysis due to a lack of trials in this population[30–34]
Uricosuric Agents[b]			
Benzbromarone[c]	Starting: 25–50 mg daily; maximal approved: 200 mg/day	Contraindicated if CrCl <20 mL/min	Contraindicated
Lesinurad[d]	Starting: 200 mg daily together with XOI; maximal approved: 200 mg/day	Contraindicated if CrCl <45 mL/min	Contraindicated
Probenecid	Starting: 250 mg twice daily; maximal approved: 2000 mg/day	Not effective if CrCl ≤30 mL/min	Contraindicated
Sulfinpyrazone[c]	Starting: 50 mg twice daily; maximal approved: 800 mg/day	Not effective if CrCl ≤30 mL/min	Contraindicated
Recombinant uricase			
Pegloticase	Starting: 8 mg IV every 2 weeks; maximal approved: 8 mg IV every 2 weeks	No dose adjustment needed	No dose adjustment needed[35]

[a] Titrate dose every 2–5 weeks to reach the serum urate target; for allopurinol, this up-titration can occur beyond the CrCl-based dose

[b] Titrate dose every 2–5 weeks to reach the serum urate target

[c] Not available in the USA;

[d] Approved for use only in combination with a xanthine oxidase inhibitor.

Abbreviations: CKD: chronic kidney disease; CrCl: creatinine clearance; HD: hemodialysis; IV: intravenous; PD, peritoneal dialysis; RRT, renal replacement therapy

Additional considerations: Losartan may be the antihypertensive drug of choice for patients with hyperuricemia and/or gout, based on its uricosuric effect. Sevelamer may be the phosphate binder of choice for patients with advanced CKD and gout, based on its urate-lowering effect[36,37]

Table 2

Suggested anti-inflammatory prophylaxis regimens to prevent gout flares

	Normal kidney function	CKD 3–5	CKD 5D (Dialysis)
Colchicine	Up to 0.6 mg every 12 hours; once daily may be sufficient	CrCl ≥30 mL/min: dosage adjustment not required; CrCl <30 mL/min: initial dose: 0.3 mg/day, caution if up-titrated; monitor closely for adverse effects	Not removed by dialysis; increased risk of myo/neurotoxicity; FDA label states 0.3 mg twice a week with close monitoring[80]
NSAID	Low-dose, e. g. naproxen 250 mg every 12 hours; lowest necessary dose	Avoid	May be considered

CKD: chronic kidney disease; CrCl: creatinine clearance; NSAID: nonsteroidal anti-inflammatory drug; FDA, US Food and Drug Administration. Note: Glucocorticoids may be considered when colchicine and NSAIDs are contraindicated, not tolerated or not efficacious; low-dose (≤10 mg/day) prednisone or prednisolone; use lowest necessary dose.

Am J Kidney Dis. Author manuscript; available in PMC 2018 September 01.

Table 3

Suggested treatment for a gout flare in patients with normal and decreased kidney function.

	Normal kidney function	**CKD 3–5**	**CKD 5D (Dialysis)**
Colchicine	1.2 mg at the first sign of a gout flare followed by 0.6 mg one hour later; then, 0.6 mg every 12 hours or followed by other gout flare therapy	Not recommended in patients already receiving colchicine for prophylaxis; **CrCl ≥30 mL/min:** dosage adjustment not required; **CrCl <30 mL/min:** consider dosage reduction; treatment course should not be repeated more frequently than every 14 days per FDA label	0.6 mg as a single dose; FDA approved label states that treatment course should not be repeated more frequently than every 14 days; not removed by dialysis
NSAID	Any NSAID in its full daily dose	**CrCl 30 to 59 mL/min:** avoid or use with caution depending on the kidney disease; **CrCl <30 mL/min:** relatively contraindicated	May be used
Steroid	0.5 mg/kg/day, followed by progressive weaning; for example, start prednisone at 30 mg/day, then reduce by 5 mg every 2 days	Dosage adjustment for CKD not required	Dosage adjustment for CKD not required
ACTH	Subcutaneous or intramuscular; treatment option for patients with restrictions to oral drugs; initial dose of 25–40 IU; doses repeated as clinically indicated	Dosage adjustment for CKD not required	Dosage adjustment for CKD not required
Interleukin-1 inhibitors	The off-label use of anakinra to treat gout flares in patients with multiple comorbidities and contraindications to the above-mentioned options has become more frequent in the US; canakinumab is approved for gout flare management by the EMA; dose: Anakinra 100 mg/day subcutaneously; Canakinumab 150 mg SC single dose, to be repeated no sooner than at least 12 weeks in patients who respond and require retreatment	CrCl <30 mL/min: For anakinra, mean plasma clearance of anakinra declined by 70–75%; consider dose reduction, as 100 mg every other day; for canakinumab, no dose reduction is needed, though clinical experience is limited	For anakinra: <2.5% of the administered dose of anakinra is removed by hemodialysis or continuous ambulatory peritoneal dialysis; consider dose reduction, as 100 mg every other day; for canakinumab, no dose reduction is needed, though clinical experience is limited

CKD: chronic kidney disease; CrCl: creatinine clearance; NSAID: nonsteroidal anti-inflammatory drug; ACTH: adrenocorticotropic hormone; IU: international units; SC: subcutaneous; FDA, US Food and Drug Administration; EMA, European Medicines Agency.

Table 4

Observational studies of urate-lowering therapy in gout and non-gout conditions, with reported results on kidney function.

Study	Study design	Setting & Participants	Exposure	Results
Whelton et al, 2011[127]	FOCUS study: open-label extension study	24 centers in US; 116 hyperuricemic gout pts with CrCl >50–79 mL/min at baseline	Febuxostat 40, 80 or 120 mg/day	The effects of SUA reduction were associated with maintenance or improvement in eGFR over a 5-year follow-up period
Pai et al, 2013[128]	Cohort study	Outpatient department of Nephrology at Nizam's Institute of Medical Sciences, Hyderabad, India; 183 pts with hyperuricemia, with eGFR <90 mL/min (mean baseline eGFR: 35.4 mL/min among the exposed and 38.9 mL/min among the non-exposed)	Allopurinol 100 mg/day vs. usual treatment	eGFR remained stable in pts treated with allopurinol while the control group presented a significant decline in kidney function, resulting in a significant difference between groups at one and two years of follow-up
Whelton et al, 2013[129]	Report of kidney outcomes from the EXCEL study	174 centers in US and Canada; 551 pts with gout and serum creatinine ≤ 1.5 mg/dL[56] or ≤ 2.0 mg/dL[57]	Only febuxostat, at any dose[a]	Greater reductions in SUA were associated with less decline in eGFR
Levy et al, 2014[116]	Cohort study	Kaiser Permanente Southern California Health Plan, US; 16,186 patients with hyperuricemia and CKD ≤ 3b	ULT (allopurinol, febuxostat, probenecid)	Individuals who achieved a SUA <6 mg/dL on ULT had 37% lower risk of kidney disease progression
Shibagaki et al, 2014[130]	Observational study	University hospitals, Japan; 70 patients with SUA ≥ 8 mg/dL and eGFR ≤ 45 mL/min	Febuxostat 10–60 mg/day, adjusted to a target SUA ≤ 6.0 mg/dL	Pts with CKD stage 3b presented a 7.4%-increase in eGFR from baseline, while those with CKD 4 and 5 showed decreased eGFR at 24 weeks; SUA level at week 24 as well as relative and absolute reduction in SUA were identified as independent variables for increase in eGFR in the multivariate analysis
Kim et al, 2015[131]	Cohort study	Dongguk University Ilsan Hospital (tertiary hospital), Goyang, Korea; 158 pts with asymptomatic hyperuricemic and CKD stage 3	ULT (allopurinol, febuxostat, benzbromarone)	Individuals on ULT had significantly less kidney disease progression, and those who achieved the target SUA with ULT dose adjustment had better kidney outcomes compared with those who were maintained on their initial dose
Singh et al, 2016[132]	Cohort study	Medicare claims data from 2006 to 2012 (5% random sample), US; 30,022 allopurinol treatment episodes with no diagnostic code for kidney failure in the previous 183 days	Allopurinol dose and duration	Higher allopurinol dose was independently protective against incident kidney failure in the elderly allopurinol users; a longer duration of allopurinol use may be associated with a decreased risk of incident kidney failure
Ma et al 2016[133]	Cohort study	Zhongshan Hospital (tertiary hospital), Shanghai, China; 106 primary gout pts with eGFR >60 mL/min and 51 healthy controls	ULT (allopurinol 300 mg/day, febuxostat 40 or 80 mg/day, benzbromarone 50 mg/day) used by 88 gout pts	CrCl showed a significant increase in the xanthine oxidase inhibitor group at six months of treatment

[a]In the EXCEL study, 1086 subjects from two prior phase 3 trials[56,57] were enrolled and randomized to either allopurinol 100–300mg, febuxostat 80mg, or febuxostat 120mg, and were permitted to switch between these three arms during the first 6 months to achieve and maintain the SUA target.[58]

CrCl: creatinine clearance; SUA: serum urate; eGFR: estimated glomerular filtration rate; ULT: urate-lowering therapy; CKD: chronic kidney disease; FOCUS, ●●●; EXCEL●●●

Table 5

Intervention studies of urate-lowering therapy in gout and non-gout conditions, with reported results on kidney function.

Trial	Study design	Participants	Intervention	Results
Gibson et al. 1982[134]	Randomized trial	59 patients with gout and normal kidney function	Allopurinol 200 mg/day + colchicine 0.5 mg twice a day vs. colchicine 0.5 mg twice a day	Allopurinol-treated patients did not present change in kidney function while those receiving only colchicine had a significant decrease in eGFR at two years of follow-up
Dahlöf et al. 2002[135]	Double-blind, randomized trial	9193 patients aged 55–80 years with essential hypertension and left ventricular hypertrophy	Losartan vs. atenolol for at least 4 years	There was no significant difference in serum creatinine between groups at the end of the trial, although the rise in SUA was lower in the losartan group
Siu et al. 2006[136]	Randomized trial	54 patients with CKD (proteinuria >0.5 g/24h and/or serum creatinine >1.35mg/dL) of varying etiologies and asymptomatic hyperuricemia	Allopurinol (100–300 mg/day) vs. conventional therapy	While SUA levels were significantly reduced in the treatment arm, there was only a non-significant trend toward a lower serum creatinine in the allopurinol group at 12 months; nonetheless, the combined end points of significant deterioration in kidney function and dialysis dependence occurred in 16% in the allopurinol group compared with 46% in the control group (P = 0.02), suggesting a renoprotective role for allopurinol
Momeni et al. 2010[137]	Double blind, placebo-controlled, randomized trial	40 patients with type 2 diabetes mellitus and diabetic nephropathy (proteinuria ≥ 500 mg/24 h and serum creatinine <3 mg/dL)	Allopurinol 100 mg/day vs. placebo	At four months, allopurinol-treated patients showed a significantly lower 24-hour urine protein compared to the control group, while serum creatinine remained stable in both groups
Kanbay et al. 2011[138]	Randomized study	105 subjects with normal kidney function: 72 with hyperuricemia + 33 normouricemic controls	Allopurinol 300 mg/day (in hyperuricemic) vs. no treatment (hyperuricemic patients and normouricemic controls)	Allopurinol use was associated with significant increase in eGFR at four months in comparison with baseline, while hyperuricemic and normouricemic controls had no significant change in the same period
Kao et al. 2011[139]	Double-blind, placebo-controlled, randomized trial	67 patients with CKD stage 3 and left ventricular hypertrophy	Allopurinol 300 mg/day vs. placebo	eGFR remained stable in both groups, with no significant difference in the change in eGFR between groups at nine months
Shi et al. 2012[140]	Open label, controlled, randomized trial	40 patients with IgA nephropathy, with proteinuria 0.15–2.0 g/24 h, albumin >3.5 g/dL, creatinine <3 mg/dL, and SUA >6 mg/dL in women and >7 mg/dL in men	Allopurinol 100–300 mg/day vs. usual care	At six months, there was no significant difference in the eGFR nor in the change in eGFR between groups
Goicoechea et al. 2010[141] and Goicoechea et al. 2015[142]	Open label randomized trial	113 patients with eGFR <60 mL/min	Allopurinol 100 mg/day (n=57) vs. and continuation of usual therapy (n=56)	After 2 years, the allopurinol arm had significantly reduced SUA, indicating adherence to therapy, with 47% lower risk of kidney disease progression compared with the control group; of the original 113 patients, 107 participants were followed-up again 5 years later, during which time 12 of 56 allopurinol users stopped treatment and 10 of 51 controls started allopurinol; while the results were consistent with the original report, these data must be interpreted with caution given the post-hoc nature, small sample size, and the non-randomized (observational) nature of the data

Trial	Study design	Participants	Intervention	Results
Kim et al. 2014[143]	Post-hoc analysis on the data derived from a phase-III, double blind, randomized trial	Patients with gout and creatinine ≤ 1.5 mg/dL	Febuxostat (40, 80 or 120 mg/day) vs. allopurinol (300 mg/day) vs. placebo	At four weeks, patients on ULT presented a significant decrease in serum creatinine levels compared to the control group; in the adjusted model, SUA changes were significantly correlated with changes in serum creatinine
Liu et al. 2015[144]	Open label randomized trial	176 individuals with type 2 diabetes mellitus, normoalbuminuria and asymptomatic hyperuricemia with normal baseline kidney function (mean eGFR of 90 mL/min)	Allopurinol dose-adjusted according to SUA vs. conventional therapy	After 3 years of follow-up, the allopurinol-treated group had significantly lower urinary albumin excretion rate and serum creatinine, along with significantly higher eGFR in comparison with the group under conventional therapy
Sircar et al. 2015[145]	Double blind, placebo-controlled, randomized trial	108 patients with CKD stages 3 and 4 with asymptomatic hyperuricemia	Febuxostat 40 mg/day vs. placebo	Patients on febuxostat experienced less eGFR decline than the placebo group at 6 months
Tanaka et al. 2015[146]	Open label, controlled, randomized trial	45 patients with CKD stage 3 and asymptomatic hyperuricemia (22 of them were on allopurinol 50–100 mg/day)	Febuxostat 10–40 mg/day, adjusted with a SUA target of <6 mg/dL vs. conventional therapy; subjects on allopurinol at baseline could either continue allopurinol or switch to febuxostat	There was no significant difference in eGFR between febuxostat and control groups at 12 weeks
Sezai et el. 2015[147]	Single blind, controlled, randomized trial	109 patients with eGFR ≤60 mL/min and SUA ≥8 mg/dL, not on ULT, undergoing cardiac surgery	Febuxostat up to 60 mg/day (up to 40 mg/day if eGFR ≤30 mL/min) vs. allopurinol up to 300 mg/day (up to 200 mg/day if eGFR ≤30 mL/min) – doses adjusted to a target SUA ≤6.0 mg/dL	There was no significant difference in eGFR between treatment groups at 1, 3 or 6 months, despite SUA being significantly lower in the febuxostat group at these time points
Saag et al. 2016[60]	Placebo- controlled blinded pilot randomized trial	96 gout subjects with moderate-to-severe kidney impairment (eGFR 15–50 mL/min/1.73m^2)	Febuxostat vs. placebo	**Primary endpoint: change in serum creatinine from baseline to month 12;** there were no significant differences in serum creatinine or eGFR between the febuxostat arms vs. placebo at 6 or 12 months of follow-up
Bose et al. 2014[148]	Systematic review and meta- analysis of 5 RCTs evaluating eGFR[134,138–141] and 3 RCTs evaluating change in serum creatinine[136,137,149]	Varying clinical conditions and kidney function stages	Allopurinol vs. placebo or conventional treatment	Change in serum creatinine from baseline favored allopurinol compared to the control arms, although the change in eGFR was not significantly different between groups; allopurinol may slow CKD progression, but adequately powered randomized trials are necessary to provide a more definitive conclusion
Kanji et al. 2015[150]	Systematic review and meta-analysis of 5 RCTs[136,137,139–141]	Varying clinical conditions in patients with CKD stages 3–5	Allopurinol vs. placebo or conventional treatment	There was a small but significant improvement in eGFR favoring allopurinol, though when limited to 3 RCTs in which the eGFR was not calculated by the meta-analysis' authors from serum creatinine data, this finding was no longer significant; this meta-analysis highlights the paucity of large, well-conducted RCTs of allopurinol's effects on kidney endpoints

eGFR: estimated glomerular filtration rate; CKD: chronic kidney disease; SUA: serum urate; ULT: urate-lowering therapy; RCT: randomized controlled trial; IgA, immuglobulin A; RCT, randomized controlled trial

Am J Kidney Dis. Author manuscript; available in PMC 2018 September 01.