Gout Management in Patients With CKD: A Review

Rochella A. Ostrowski

The management of gout in patients with chronic kidney disease (CKD) can be challenging due to multiple factors. These include limitations on the type or doses of medications used. Although limitations or exclusions of some treatment options are warranted, others that are traditionally followed, such as the doses used for urate-lowering therapies such as allopurinol or febuxostat, may lead to undertreatment of gout. In this review, guidelines from consensus groups are discussed with a focus on management of gout in patients with CKD and appropriate dose adjustments beyond traditional kidney-dosed limits. Studies in the literature with regard to risk factors for allopurinol hypersensitivity syndrome are reviewed, including HLAB*5801 allele testing. Additionally, current evidence that allows providers to optimize both the effectiveness and safety of gout management in the setting of CKD, such as the "start-low-go-low" approach, are reviewed as well as considerations for kidney transplant recipients. Although there is a potential role of sodium/glucose cotransporter 2 inhibitors in lowering serum urate, it is limited in CKD. Finally, the use of immunomodulators to improve outcomes for pegloticase, a pegylated form of uricase, shows promise for increasing the utility of pegloticase in cases where it is warranted.

Complete author and article information provided before references.

Correspondence to R.A. Ostrowski (rostrowski@lumc.edu)

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Chronic kidney disease (CKD), a condition associated with gout,[1] was reported in 697.5 million persons globally in 2017 with a global prevalence of 9.1%.[2] In the United States, this prevalence is even higher at 13.9%,[3] affecting 35.5 million individuals.[4] Gout, an inflammatory arthritis involving an immune response to monosodium urate crystals, causes acutely painful and swollen joints, potentially leading to joint erosions. In 2020, 55.8 million people globally had gout, and this burden is estimated to reach 95.8 million by 2050.[5]

Gout is more common in patients with CKD, with a prevalence of 4%, 6% to 10%, 11% to 13%, and >30% for patients with stages 1, 2, 3, and 4 CKD, respectively, compared with 2% to 3% in persons without CKD.[6] Treating gout in CKD is important due to its prevalence, but options can be limited, and patients are therefore often undertreated. This review examines the existing data and guidelines pertaining to the management of gout in patients with CKD. A recent publication in *Kidney International* serves as another valuable review and offers guidance that complements the material reviewed here.[7]

Which Patients Need Urate-Lowering Therapy?

Long-term therapy for gout centers around lowering serum urate (SU) levels. Although 75% to 90% of patients with gout are underexcreters of uric acid rather than overproducers,[8] xanthine oxidase inhibitors (allopurinol or febuxostat) are first-line therapies used more often than uricosuric agents (probenecid or benzbromarone), especially in CKD.

There are multiple guidelines for long-term gout management. The American College of Rheumatology (ACR) recommends urate-lowering therapy (ULT) for patients with ≥1 subcutaneous tophi, radiographic gout, or ≥2 gout flares annually.[9] ULT is not recommended for patients who are experiencing their first gout flare except for those with moderate-to-severe CKD (CKD stage ≥3), SU > 9 mg/dL, or urolithiasis.

The European Alliance of Associations for Rheumatology (EULAR) recommends ULT in patients with recurrent gout flares, tophi, urate arthropathy, and/or urolithiasis. They additionally recommend ULT after diagnosis in patients younger than 40 years or in patients with very high SU levels (>8.0 mg/dL).[10] EULAR also recommends ULT for patients with CKD, hypertension, ischemic heart disease, or heart failure.

For patients with normal kidney function, the ACR and EULAR advise starting allopurinol at ≤100 mg/day and increasing by 100 mg every 2-4 weeks until the SU target of <6 mg/dL (360 μmol/L) is reached. A lower SU target (<5 mg/dL) is recommended for patients with severe gout (tophi, chronic arthropathy, frequent attacks). If the SU target cannot be reached despite the maximum dose approved by the US Food and Drug Administration (FDA) of 800 mg, allopurinol should be switched to febuxostat or a uricosuric or should be combined with a uricosuric. However, the ACR guidelines specify febuxostat as the next treatment of choice over uricosurics. Uricosurics are not recommended for patients with CKD. Indefinite treatment is recommended because 38.9% of patients experience recurrence of gout when ULT is withdrawn.[11] Figure 1 summarizes recommendations for ULT in the setting of CKD.

In 1984, Hande et al[12] described a severe cutaneous reaction to allopurinol in 78 patients with CKD, a condition now known as allopurinol hypersensitivity syndrome (AHS), a potentially fatal reaction characterized by rash, eosinophilia, leukocytosis, fever, hepatitis, and kidney failure, with an incidence of approximately 0.1%.[13] Rashes in AHS can take the form of toxic epidermal necrolysis, exfoliative dermatitis, or Stevens-

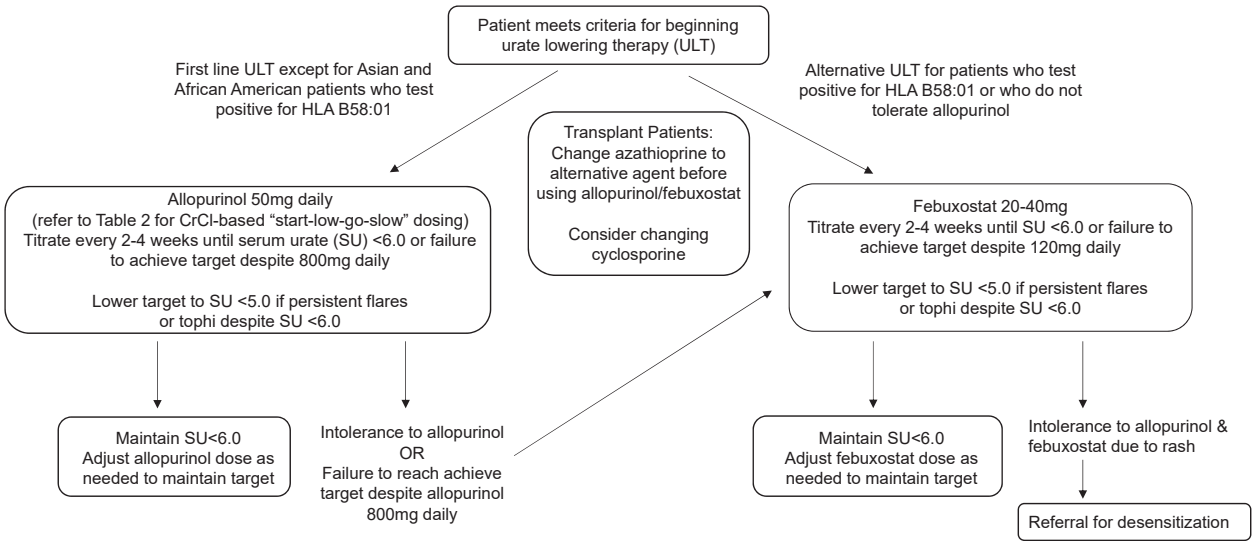

Figure 1. Long-term management of gout in patients with chronic kidney disease. Abbreviations: CrCl, creatinine clearance; SU, serum urate; ULT, urate-lowering therapy.

Johnson syndrome. Hande et al[12] included guidelines for kidney-limited allopurinol dosing (Table 1) to protect patients from AHS, but adherence to the Hande group's dose limits may lead to undertreatment of gout.[14,15] In a study of patients with gout taking allopurinol, the SU target was achieved in only 23.3%, 20.2%, and 18.8% of those with stages 2, 3, and 4 CKD, respectively.[14] In another study, 49.4% of patients with uncontrolled gout had CKD, compared to 32.4% of those with controlled gout.[15]

Timely monitoring of SU and continuous treatment to achieve targets is necessary for effective treatment, even in the setting of CKD. Yet in a 4-year evaluation of veterans with gout receiving new allopurinol prescriptions, only 46% were given continuous prescriptions, and only 20% reached target SU.[16] Twenty-four percent of patients had SU levels checked within 6 months,[17] and 61% had no SU checked at all during the study period.[16] In 127 patients who had postprescription SU levels not at target, only 37% of patients not at SU target had adjustments in allopurinol doses.[16]

Table 1. 1984 Recommendations for Creatinine Clearance–Based Allopurinol Dosing

Creatinine Clearance	Recommended Dose of Allopurinol
0	100 mg every 3 days
10	100 mg every 2 days
20	100 mg daily
40	150 mg daily
60	200 mg daily
80	250 mg daily
100	300 mg daily
120	350 mg daily
140	400 mg daily

Based on information in Hande et al.[12]

Treating to Target in Patients With CKD

There is some variation between guidelines on the escalation of allopurinol dosing for gout patients with CKD. EULAR guidelines recommend restricting allopurinol to doses based on creatinine clearance (CL_{cr}) and considering febuxostat as an alternative.[9,18] ACR guidelines recommend gradual escalation of allopurinol above CL_{cr}-based dosing up to the maximum FDA-approved doses to achieve target SU.[8]

Most studies showing that patients with CKD tolerate higher doses have been published in the last 15 years. A randomized controlled trial evaluated the safety of treat-to-target approaches in CKD, including patients with $CL_{cr} < 30$ mL/min.[19] Patients on CL_{cr}-based allopurinol doses not at target SU were randomized to continue their current dose or escalate until achieving SU ≤ 6 mg/dL. At the conclusion of the study, 69% with dose escalations achieved target SU, and dose escalation was well tolerated.[19] Additionally, 28.8%, 34.8%, and 73.1% of patients required ≤100 mg, 101-200 mg, and >200 mg above CL_{cr}-based allopurinol dosing, respectively. The highest amount above the CL_{cr}-based dose required by any patient was 700 mg per day.[20]

Although allopurinol is often limited to 300 mg, a subset of patients need higher doses. Allopurinol requirements were studied in 400 patients recruited into the multicenter 2014 Febuxostat versus Allopurinol Streamlined Trial (FAST).[21] In order to achieve the target SU, 67% of patients on allopurinol 100 mg daily required uptitration compared with 16% who were already taking 300 mg. The highest dose given to a patient with CKD was

500 mg—much higher than would traditionally have been given—supporting the safety of allopurinol dose escalation in CKD.

The Start-Low-Go-Slow Approach

Doses for initiating ULT in gout have varied with trends of medical practice, but the most recent consensus is start-low-go-slow. This approach is attractive not only for patients with CKD but for all patients with gout because it decreases flares in early treatment, a phenomenon that can frustrate patients and lead to noncompliance. The start-low-go-slow approach can also decrease the risk for AHS.

In a 2023 randomized, double-blind, controlled trial conducted by Stamp et al,[22] 200 patients began ULT with the start-low-go-slow approach at 50-100 mg allopurinol daily titrated monthly by 50 mg in patients with an estimated glomerular filtration rate (eGFR) of >60mL/min/1.73 m^2 to a SU level of <6 mg/dL and were randomized to colchicine prophylaxis or placebo. Placebo was noninferior to colchicine in preventing gout flares in the first 6 months of ULT. This approach differs from previous practices of starting allopurinol at 300 mg and may decrease the need for prophylaxis.[22] This observation has also been noted with febuxostat.[23]

Another reason to begin allopurinol at lower doses is to reduce the risk for AHS, which is often seen with higher initial doses. In a case-control study of patients with gout who developed AHS, higher starting doses of allopurinol, corrected for eGFR, led to a higher incidence of AHS.[24] An odds ratio of 23.2 was observed for the highest quintile of starting dose per unit eGFR, and 91% of cases versus 36% of controls started allopurinol at ≥1.5 mg/unit eGFR. The authors suggest starting allopurinol at 1.5 mg/unit eGFR (Table 2) followed by monthly titration as tolerated.

Table 2. Proposed Starting Doses for Allopurinol in a Start-Low-Go-Slow Approach

eGFR, mL/min/1.73 m^2	Allopurinol Starting Dose	Dosing Interval
<5	50 mg	Once weekly
5-15	50 mg	Twice weekly
16-30	50 mg	Every 2 days
31-45	50 mg	Daily
46-60	50 mg and 100 mg	Each on alternate days[a]
61-90	100 mg	Daily
91-130	150 mg	Daily[b]
>130	200 mg	Daily[b]

Based on information in Stamp et al.[13,22] Abbreviation: eGFR, estimated glomerular filtration rate.
[a]Alternate dosing would occur as 50 mg every other day, alternating with 100 mg every other day.
[b]Although these recommendations are proposed for dosing based on eGFR in the publications by Stamp et al, note that the current guidelines of the American College of Rheumatology and European Alliance of Associations for Rheumatology do not recommend initial allopurinol dosing greater than 50 to 100 mg daily.

HLA-B*5801 and Allopurinol Hypersensitivity Syndrome

Although the starting dose for allopurinol is one contributor to AHS, other factors play a role in AHS, including genetics and CKD.[25] The presence of the HLA-B*5801 allele is highly associated with AHS in some Asian populations,[24] carrying an odds ratio of 580, 348.3, and 65.6 in Han Chinese,[25,26] Thai,[27] and Japanese[28] patients, respectively, for AHS.

The HLA-B*5801 allele is also associated with AHS in Korean populations.[29,30] However, because only 18% of HLA-B*5801-positive patients experience AHS, studies have explored other factors.[31] The additional presence of the HLA-A*2402 allele confers an odds ratio of 12.0 for drug reaction with eosinophilia and systemic symptoms (DRESS) compared with allopurinol-tolerant HLA-B*5801 carriers. That odds ratio increases to 66.0 when another gene marker, DRB1*1302, is also present.

The prevalence of HLA-B*5801 in patients with AHS is lower in European patients compared with Han Chinese patients.[32] In the United States, the prevalence of HLA-B*5801 is 0.7% in Whites and Hispanics, 3.8% among African Americans, and 7.5% among Asians.[33]

Although the early data on genetic risk factors for AHS centered on Asian populations, African Americans have since been added as an at-risk group.[9,34,35] In a study of 1,366 African American patients genotyped for kidney transplantation, 6% carried the HLA-B*5801 allele, and 1 patient was listed as having a severe reaction to allopurinol.[33] In a study of 606 hospitalizations for severe cutaneous adverse reactions in the setting of ULT, hospitalization rate ratios for these reactions were 11.9 and 5.0 among Asian and Black patients, respectively, compared with White patients.[35] The ACR guidelines recommend HLA-B*5801 testing before initiating allopurinol for patients of Southeast Asian descent and African American patients.[9,33] HLA-B*5801 testing should also be performed in Asian populations such as Han Chinese, Korean, and Japanese.

The delayed onset of AHS, which occurs at a mean of 30 days after allopurinol initiation, appears to be immunologically mediated. Lower doses of allopurinol may lead to desensitization for individuals who are genetically vulnerable or at risk for drug accumulation such as patients with CKD.[24]

Alternative Urate-Lowering Therapies

Febuxostat

When patients cannot tolerate allopurinol or reach target SU with optimized allopurinol doses, febuxostat is an alternative ULT. Unlike allopurinol and its metabolite, oxypurinol, which are cleared by the kidneys,[36] febuxostat is metabolized in the liver.[37] For patients with CKD, the starting dose for febuxostat is 20-40 mg daily,[7] titrated to achieve target SU up to 120 mg per day. It is effective for

lowering SU and decreasing the incidence of gout flares,[38] an observation also seen in patients with CKD.[39] However, the STOP Gout Trial, which enrolled 940 participants, showed allopurinol to be noninferior to febuxostat in controlling gout flares,[40] including in patients with CKD.[41]

Given the association of CKD with cardiovascular disease,[42] it is important to note that the FDA issued an alert in 2017 to evaluate the cardiovascular risk of febuxostat based on preliminary results from the Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout trial (CARES). The primary end point of the study was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or unstable angina with urgent revascularization. However, this outcome was found to reach statistical significance for noninferiority between the febuxostat and allopurinol groups (10.8% and 10.4% of patients, respectively; $P = 0.002$ for noninferiority).[43] Additional studies have shown febuxostat to have comparable outcomes compared with allopurinol with respect to cardiovascular events and death from cardiovascular causes.[44-46]

As for the risk of severe cutaneous adverse reactions, 9.1% of patients who previously had experienced skin reactions on allopurinol also developed skin reactions on febuxostat.[47] Only 2.5% of patients developed skin reactions on febuxostat who had not done so with allopurinol, and none of the reactions were severe. In the event that a patient develops a skin reaction to both allopurinol and febuxostat but is not a candidate for uricosuric agents, allopurinol desensitization is an option that can be carried out under the guidance of an allergy specialist.

Uricosuric Agents and Pegloticase

Despite uric acid underexcretion's role as the predominant mechanism for hyperuricemia in gout, uricosurics are not recommended by the ACR as first-line ULT for patients with moderate-to-severe CKD (stage ≥3).[9] By contrast, EULAR recommends uricosurics alone (particularly benzbromarone) or in combination with allopurinol in patients who fail to achieve target SU with allopurinol alone. Probenecid is the only available uricosuric in the United States; benzbromarone, more effective than probenecid,[10,48] is available in Europe and other countries. Another uricosuric, lesinurad, was removed from the market in February 2019.[49] The frequent choice of xanthine oxidase inhibitors over uricosurics by physicians, combined with the cost of lesinurad, led to its inability to maintain a market. Probenecid has reduced efficacy and limited safety data in patients with CKD and is not recommended over xanthine oxidase inhibitors.

Pegloticase is a pegylated form of uricase that catalyzes the oxidation of uric acid into the more soluble end product allantoin. EULAR guidelines recommend pegloticase for patients with severe debilitating chronic tophaceous gout and poor quality of life who have failed at maximal doses of other ULT agents.[10] Kidney dosage adjustment is not needed. However, allergic or infusion reactions can occur and correlate with loss of response[50] and development of immunogenicity against pegloticase.[51] Concomitant use of immunomodulators like methotrexate, mycophenolate mofetil, leflunomide, and azathioprine increase pegloticase response by attenuating the development of antipegloticase antibodies.[52] Methotrexate markedly increases pegloticase response rates, decreases antibody positivity, and reduces infusion reactions.[53] Although it can be given with dose adjustments in mild CKD, it should be avoided in patients with severe CKD ($CL_{cr} < 30$ mL/min). Mycophenolate mofetil is associated with an 86.4% response rate compared with 40% for placebo,[54] and azathioprine use is associated with a 60% response.[55] Dose adjustment for CKD is not required with leflunomide, but safety data in CKD are limited.[56]

Sodium/Glucose Cotransporter 2 Inhibitors in Gout

Sodium/glucose cotransporter 2 (SGLT2) inhibitors can lower SU. These agents can reduce intracellular levels of hypoxanthine and reduce the oxidative stress that contributes to the expression and activation of xanthine oxidase, which can interfere with uric acid production.[57] SGLT2 inhibitors have also been shown to enhance urate excretion in patients with diabetes and heart failure.[58-60]

In the EMPEROR-Reduced trial (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction), the SGLT2 inhibitor empagliflozin, was associated with a 1.12 mg/dL decrease in SU levels and a 32% reduction in events of clinically relevant hyperuricemia, defined by the investigators as gout flares, gouty arthritis, or initiation of ULT.[58] In a meta-analysis of 43 randomized controlled trials that examined the effect of SGLT2 inhibitors on SU conducted by Yip et al,[61] nondiabetic patients experienced a lowering of SU levels by 91.38 μmol/L (5.44 mg/dL) compared with placebo. This effect was smaller in patients with diabetes at 31.48 μmol/dL (1.87 mg/dL) and did not reach significance in patients with type 2 diabetes and CKD.

The modest decrease in SU levels with SGLT2 inhibitors should be weighed in the selection of medications for patients with diabetes and gout. However, this selection should take into account the diminished effect observed in patients with higher degrees of hyperglycemia and CKD.[61,62]

Treatment of Gout Flares in Patients With CKD

Management of acute flares in settings of CKD also differs from the standard approach (Fig 2). The ACR recommends colchicine, nonsteroidal anti-inflammatory drugs (NSAIDs), or glucocorticoids (oral, intra-articular, or intramuscular), with oral glucocorticoids often being the first choice for practitioners in patients with CKD. Interleukin-1 (IL-1) inhibitors such as anakinra and adrenocorticotropic hormone are options, but they are not

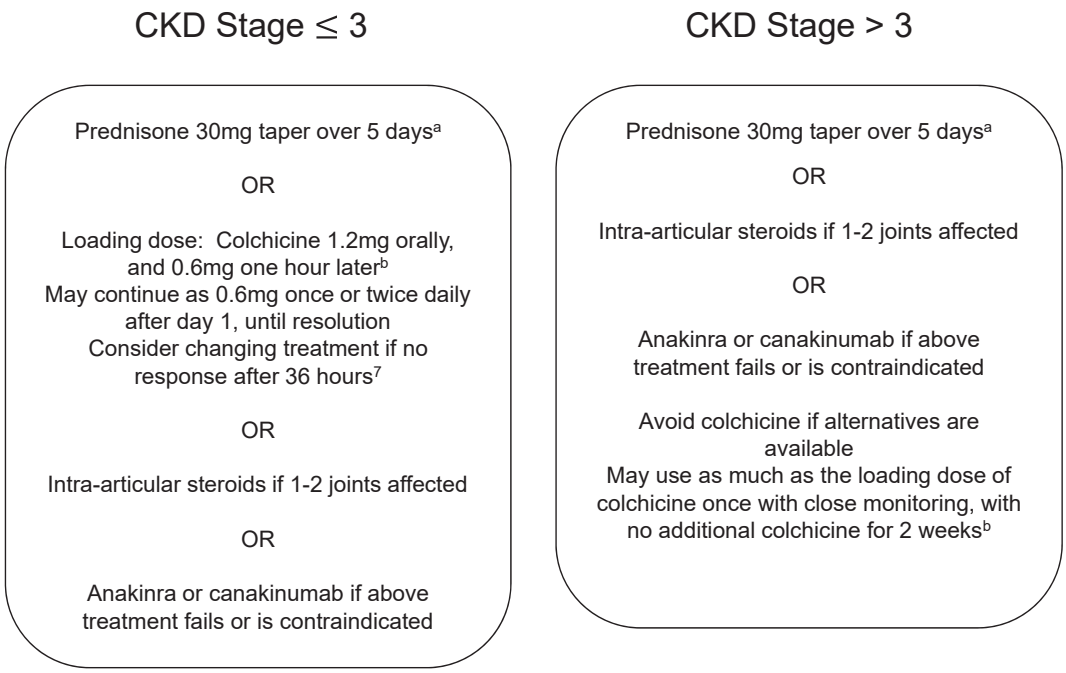

Figure 2. Treatment of gout flare in patients with CKD. [a]Prednisone doses may vary based on experience of clinician and responses of individual patients. In subsequent flares, a shared decision making process based on previous responses of the patient to prednisone may warrant doses as high as 50-60 mg and courses as long as 15 days. Equivalent corticosteroid doses may be given intravenously in patients unable to take oral medications. [b]Avoid use of colchicine for gout flares in any patients with CKD who have already been receiving prophylactic colchicine. Abbreviation: CKD, chronic kidney disease.

considered first-line therapies.[9] Because NSAIDs are contraindicated in CKD, treatments are limited to colchicine, oral steroids, or arthrocentesis and steroid injections.[10]

Colchicine administration is recommended within 12 hours of symptom onset.[10,63] The dosage for colchicine is 0.6 mg per tablet in the United States and 0.5 mg in European countries. Current recommendations for patients with normal kidney function are 2 tablets of colchicine followed by 1 tablet 1 hour later.

Dose adjustment of colchicine is not required in mild (CL_{cr} 50-80 mL/min) to moderate (CL_{cr} 30-50 mL/min) CKD. However, in severe impairment (CL_{cr} < 30 mL/min), treatment with colchicine should not be administered more than once every 2 weeks. There are differing recommendations regarding the use of colchicine loading in patients with severe CKD, including patients receiving dialysis, ranging from the general recommendation of avoiding the drug[10,64,65] to as much as the full loading dose.[7] In these scenarios, the author prefers corticosteroids, which avoid the potential for adverse effects seen with colchicine. Colchicine use for gout flares is not recommended in patients with any stage of CKD who are already receiving colchicine as prophylaxis.[66]

Regardless of kidney function, colchicine, a substrate for CYP3A4 and P-glycoprotein, should not be used in patients who are receiving strong P-glycoprotein and/or CYP3A4 inhibitors such as cyclosporine or clarithromycin.[10] These drug interactions increase the risk for colchicine toxicity and may lead to pancytopenia, multiorgan failure, and cardiac arrhythmias.[67]

Other treatment recommendations in the EULAR guidelines include oral prednisolone of 30-35 mg for 5 days and intra-articular corticosteroids.[10] The ACR guidelines are similar, adding parenteral options when oral forms are not possible. They also leave corticosteroid dosing to the discretion of the provider.[9] Canakinumab, an IL-1 inhibitor given subcutaneously, is an effective treatment for gout flares,[68] but it should be reserved for patients with frequent flares in whom first-line therapies are ineffective or contraindicated. Its duration of effect is 12 weeks, and it can be cost-prohibitive. Although there are no renal dose adjustments in the manufacturer's labeling, canakinumab has not been studied in patients with CKD. Anakinra, an IL-1 inhibitor with a much shorter half-life, has been used off-label in gout flares at 100 mg subcutaneously once daily until symptom improvement (usual duration of 3-5 days)[69] Alternate day dosing should be considered when CL_{cr} is <30 mL/min,[70] but retrospective observations suggest that anakinra for gout flares may be a safe option for patients with stage 4-5 CKD or kidney transplantation.[71]

Prophylaxis for Gout in Patients With CKD

To minimize the recurrence of flares during the initial phases of ULT, the ACR guidelines recommend prophylaxis with colchicine, NSAIDs, or prednisone/prednisolone

for 3 to 6 months and continuation if needed.[9] EULAR guidelines recommend prophylaxis during the first 6 months of ULT with colchicine, renal dosed as needed,[10] or NSAIDs. NSAIDs are not recommended in patients with CKD, and there are limited conclusive data on the efficacy or safety of gout flare prophylaxis for patients with advanced CKD.[72]

Prophylactic dosing of colchicine is 0.6 mg once or twice daily for patients with normal kidney function, once daily in CKD stage 3 (CL_{cr} 30-60 mL/min), and once every 2 to 3 days or 0.3 mg daily in CKD stage 4 (CL_{cr} <30 mL/min).[7] Colchicine should be avoided in patients with CL_{cr} <10 mL/min, treated with hemodialysis, clinically significant hepatic or hepatobiliary dysfunction, or combined hepatic and kidney disease. A half-dose reduction has also been advised for patients ≥70 years of age.[8]

Although low-dose prednisone (5 to 7.5 mg daily) has not been studied in clinical trials, it has been used in patients who are intolerant to colchicine and is often a preferred agent for patients with severe CKD. When patients have not experienced recurrent gout flares in months leading up to ULT initiation, the author offers patients the start-low-go-slow approach as a treatment option without prophylaxis.

Special Considerations for Transplant Patients

In general, long-term and prophylactic management, as well as treatment of acute flares of gout are similar in patients who have received kidney transplants. The criteria for diagnosis and initiation of treatment do not change in transplant recipients. However, important considerations related to medication selection arise when posttransplant regimens include azathioprine. Concomitant use of allopurinol or febuxostat with azathioprine carries a risk of severe cytopenias; although the recommendation to decrease azathioprine doses by at least two-thirds when using it with allopurinol may decrease the risk of myelosuppression, it does not eliminate that risk.[73] When possible, a change from azathioprine to another transplant medication such as mycophenolate mofetil can circumvent the risk posed by interactions between azathioprine and allopurinol.

Another factor to consider is the use of cyclosporine in posttransplant regimens. Cyclosporine decreases urate clearance in the kidneys and is associated with increased SU levels and the development of gout.[74] In transplant patients who develop gout after initiating therapy with cyclosporine, shared decision making should weigh the risks and benefits of continuing cyclosporine against substituting an alternative agent. A change in treatment should especially be considered if the use of cyclosporine is thought to be a significant reason for the development of gout in the transplant recipient. Tacrolimus, another calcineurin inhibitor, may carry a decreased risk of hyperuricemia and gout compared with cyclosporine,[75] but there are conflicting reports as to whether it confers a lower risk of gout.[76] As reviewed earlier, cyclosporine use with colchicine increases the risk for colchicine toxicity.

Future Considerations for Gout Management

Aside from the pharmacologic considerations for patients with CKD which have been discussed in this review, dietary and lifestyle modifications to address comorbidities that increase the risk of gout are also important.

Future considerations for studies should include the variability with which patients are treated with steroids for acute flares,[77] and these should include patients with CKD. Additionally, although the guidelines recommend lifelong therapy, there is no consensus regarding what SU level should prompt a decrease in ULT dosage, although EULAR guidelines recommend against long-term continuous SU levels < 3 mg/dL.[10] SU levels may decrease markedly in the setting of concomitant medications changes or improvement of comorbidities. This is especially true in patients whose kidney function changes significantly after having established ULT. In the author's experience, patients whose SU levels are consistently less than 4 mg/dL are offered the option to decrease allopurinol no further than 50 mg at a time (or 40 mg for febuxostat) in a shared decision making process. There is little to no literature on the success of this approach, and trials are warranted to further evaluate this possibility for patients, including those with CKD.

Awareness of existing and emerging evidence on safe and effective gout management for patients with CKD should lead to a decrease in disease burden and improvement in quality of life for this patient population.

Article Information

Author's Full Name and Academic Degrees: Rochella A. Ostrowski, MD, MS.

Author's Affiliations: Loyola University Medical Center, Maywood, Illinois; and Edward Hines Jr Hospital, Veterans Administration, Hines, Illinois.

Address for Correspondence: Rochella A. Ostrowski, MD, MS, Loyola University Medical Center, Rheumatology, 2160 S First Ave, Maywood, IL 60153. Email: rostrowski@lumc.edu

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