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Management of Gout in the Presence of Chronic Kidney Disease

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Management of acute and chronic gout is challenging in the setting of chronic kidney disease (CKD). Common gout treatments have been associated with severe adverse events in patients with renal dysfunction.[1-5] The recently published guidelines from the American College of Rheumatology (ACR) provide some guidance on the treatment and prevention of gout in CKD .[6,7] However, many of the new recommendations are based on consensus and expert opinion (Level C) and are not evidence based. The purpose of this newsletter is to provide direction on the management of gout in patients with CKD, including pertinent updates from the new guidelines.

Acute Management of Gout

The primary treatment options for acute gout include non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, and corticosteroids. Pharmacologic treatment should begin within 24 hours of onset of an acute gout attack (Level C). The ACR guidelines do not recommend one therapeutic class over another due to lack of robust evidence for any particular drug class. Drug selection should take into account patient comorbidities.[7]

NSAIDs are one of the first-line modalities in the treatment of acute gout.[7] All NSAIDs have similar efficacy when initiated early at appropriate doses.[1,2] The ACR guidelines do not recommend one NSAID over another. However, naproxen (Level A), indomethacin (Level A), and to a lesser extent sulindac (Level B), have the most evidence of efficacy.[7] All NSAIDs can cause acute renal injury and worsen CKD. Other renal side effects of NSAIDS include: acute tubular necrosis, acute interstitial nephritis, proteinuria, and hyperkalemia. Although the guidelines do not provide specific dosing recommendations for NSAIDs in patients with renal impairment, it is suggested to start with low doses.[7] In certain patients who require aggressive inflammatory doses of NSAIDs for acute gouty flares, CKD may pose a challenge. Risks versus benefits should be considered when prescribing NSAIDs in patients with renal impairment. Those at risk of developing NSAID-induced renal insufficiency should be monitored every 2 to 4 weeks for changes in serum creatinine.[3] NSAIDs are generally not recommended in Stage 4 or 5 CKD and should be used with caution or avoided in patients with congestive heart failure, a history of active peptic ulcer disease, hepatic dysfunction, and in patients taking anticoagulants.[7,3]

Oral colchicine is a good option in patients who are unable to tolerate NSAIDs or high doses of corticosteroids, however, there are significant concerns in using colchicine in those with CKD.[8] Colchicine is only recommended if it can be initiated within 36 hours of an acute gout attack (Level of Evidence C).[7] The clearance of colchicine is significantly reduced in CKD, and prolonged use can lead to colchicine-induced axonal neuropathy, neutropenia, and myopathy. The guidelines refer to the FDA-approved product labeling for dose adjustments in patients with CKD and recommend that dose adjustments be individualized. In patients with severe renal impairment (CrCl <30ml/min), the usual acute treatment doses can be given, but dosing should not be repeated more than once every two weeks.[10] In dialysis patients, a one time 0.6 mg dose is recommended, and dosing should not be repeated more than once every two weeks.[10] Dose reduction or drug avoidance should be considered with concomitant use of strong inhibitors of cytochrome P450 3A4 and of P-glycoprotein inhibitors.[7,10] Colchicine should also be used with caution in elderly patients because creatinine levels may appear normal despite significant underlying renal impairment.[3] A recent review found an association between colchicine and rhabomyolysis, acute pancreatitis, and myopathy in patients with CKD.[3]

The guidelines do not specify corticosteroids as an alternative in patients with CKD, however, they are the preferred treatment option for management of acute gout attacks in CKD due to renal concerns with NSAIDs and colchicine. Oral, intramuscular, or intravenous steroids can provide relief for acute gout. The number of joints with active arthritis should be considered when selecting the route of corticosteroid therapy.[7] Prednisone should be initiated at 0.5 mg/kg per day for 5 to 10 days and then stopped (Level A).[7] Alternatively, a dose of 0.5 mg/kg per day can be used for 2 to 5 days, tapered for 7 to 10 days, and then stopped (Level C).[7] Dosing of intraarticular corticosteroids should be based on the size of the joint involved (Level B).[7] Intraarticular corticosteroids may be used in combination with oral corticosteroids, NSAIDs, or colchicine (Level B).[7]

The ACR guidelines recommend combination therapy for severe acute gout attacks and for patients not responding adequately to initial pharmacologic monotherapy (Level C).[7] Potential combinations include: 1) colchicine and an NSAID 2) colchicine and an oral corticosteroid or 3) intraarticular corticosteroid and any other treatment modality.[7] NSAIDs and systemic corticosteroids are not recommended in combination due to increased risk of gastrointestinal (GI) toxicity.[7]

Chronic Management of Gout/Hyperuricemia

Chronic hyperuricemia can trigger acute gouty attacks. Long term prophylaxis with urate lowering therapy (ULT) is indicated to maintain serum uric acid levels below 6mg/dl (ideally 5mg/dl).[6,7,11,12] First-line ULT agents are the xanthine oxidase inhibitors (XOIs) allopurinol and febuxostat, with no preference given to one agent over the other (Level A).[6] Second line alternatives are uricosurics, such as probenecid (Level B).[6]

Traditionally, the starting dose of allopurinol in patients with preserved renal function has been 300 mg/day. However, the ACR guidelines now recommend that starting doses be no greater than 100 mg/day (Level B).[6] In stage 4 or worse CKD, the starting dose should be 50 mg/day (Level B).[6] Initiation of therapy with lower doses can potentially reduce the likelihood of early gout flares after ULT initiation and allopurinol-induced hypersensitivity reactions. It is recommended to gradually titrate up doses every 2 to 5 weeks to reduce serum urate to target levels (Level C).[6] Doses can be increased above 300 mg/day to meet serum urate goals, even in patients with renal impairment as long as appropriate monitoring and patient education is provided.[6] This recommendation is based on evidence that doses of 300 mg/day or lower failed to decrease uric acid levels below 6 mg/dl or 5 mg/dl.[12] The common algorithm used to adjust doses based on renal function is not evidence based and is not recommended in the new guidelines.[6,13]

Allopurinol is well tolerated, however 2% of patients develop a mild rash.[1] In contrast, severe allopurinol hypersensitivity syndrome (AHS) is a rare but serious side effect and is associated with significant mortality (20-25%).[6] AHS includes symptoms of Stevens-Johnson syndrome and toxic epidermal necrolysis, as well as systemic disease features including eosinophilia, vasculitis, rash and end-organ disease.[14,15] Renal impairment and concomitant thiazide diuretic use can increase the risk of AHS. Although no studies have shown an association between allopurinol doses and the development of AHS,[14] it is recommended to initiate allopurinol at low doses and gradually increase the dose to mitigate the risk of AHS.[6] In select patients who are at a higher risk for AHS (e.g., Koreans with stage 3 or worse CKD, and Han Chinese and Thai), consideration should be given to polymerase chain reaction (PCR)-based HLA-B*5801 screening before initiating therapy (Level A).[6] In patients using allopurinol, the ACR guidelines strongly recommend diligent monitoring for hypersensitivity and other side effects such as pruritus, rash, elevated liver function tests (LFTs), and eosinophilia.[6]

Another ULT first-line option for the treatment of chronic gout is febuxostat. In contrast to allopurinol, febuxostat is metabolized by hepatic glucuronidation and oxidation.[16] Renal elimination plays only a small role in febuxostat pharmacokinetics, therefore, it does not require renal dose adjustment in mild to moderate CKD.[16,17,18] Evidence is lacking on the safety of febuxostat in stage 4 CKD or worse, and there is no safety data regarding febuxostat in patients with a history of allopurinol hypersensitivity.[16,19] The usual starting dose of febuxostat is 40 mg/day with a maximum FDA-approved dose of 80 mg/day.[16] The ACR guidelines endorse titrating up to 120 mg/day (used outside USA) in patients with refractory gout despite FDA labeling.[6]

When managing gout on a chronic basis, it is reasonable to substitute one XOI for another in patients who experience intolerable side effects, or if the serum urate goal is not achieved with the current XOI (Level C).[6] The ACR guidelines recommend regular monitoring of serum urate every 2 to 5 weeks during ULT titration and continuing measurements every 6 months once the serum urate target is achieved.[6]

Although the guidelines do not preferentially recommend one XOI over another, febuxostat treatment is significantly more expensive than allopurinol. A one month supply of febuxostat 40 mg/day costs approximately $192 compared to a month supply of allopurinol 300 mg/day costing approximately $24.[20] The National Institute for Health and Clinical Excellence (NICE) recommends that febuxostat be reserved for patients intolerant to allopurinol, due to cost differences.[21]

The uricosuric agent probenecid is considered an alternative first-line ULT option in patients with a contraindication or intolerance to a XOI (Level B).[6] Probenecid is not recommended in patients with a creatinine clearance less than 50 ml/min and shown to be ineffective when GFR is 30 mL/min or less.[3,6] The guidelines suggest other agents with uricosuric effects, such as fenofibrate or losartan, should be utilized (Level B).[6] In disease refractory to XOIs, the addition of an agent with uricosuric effects can be considered (Level B).[6]

Gout Attack Prophylaxis

Prophylaxis against acute flares is advised during the initiation of ULT because rapid lowering of serum urate levels is associated with gout flares. The ACR guidelines recommend prophylaxis with low-dose colchicine (0.6 mg once or twice a day) or low-dose NSAIDs (naproxen 250 mg orally twice daily) as acceptable first-line options, with a higher evidence level for colchicine (Level A).[7] In patients with severe renal impairment (CrCl <30ml/min), the recommended starting dose of colchicine is 0.3 mg/day. For patients on dialysis, the starting dose is 0.3 mg twice a week.[10] In CKD even reduced doses of colchicine can lead to toxicity.

Despite limited data, low-dose (≤ 10 mg daily) prednisone or prednisolone are recommended if first-line agents fail to prevent acute attacks (Level C).[7] The risks associated with prolonged corticosteroid therapy should be considered.[7] The length of therapy is determined by the presence of tophi and the attainment of target serum urate levels. The ACR guidelines recommend continuation of prophylactic therapy for the greater of the following: 6 months duration (Level A), 3 months after achieving target serum urate levels in patients without tophi (Level B) or 6 months after achieving target serum urate levels in patients where there has been resolution of tophi (Level C).[7]

Non-pharmacologic Therapy

The ACR guidelines do not recommend complimentary therapies such as cherry juice, ginger, flaxseed, or charcoal.[7] Topical ice can be used in conjunction with other pharmacological therapies (Level B).[7] Lifestyle and dietary measures such as losing weight, avoiding foods rich in purines, smoking cessation, limiting alcohol consumption, and consuming vegetables are encouraged by the guidelines.[6,7]

Evidence Grades for Recommendations
Level A: Supported by multiple (i.e., ≥1) randomized clinical trials or meta-analyses
Level B: Derived from a single randomized trial, or nonrandomized studies
Level C: Consensus opinion of experts, case studies, or standard-of-care

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