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A Literature Review Examining the Use of Allopurinol in the Treatment of Gout for Patients with Chronic Kidney Disease

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Opportunity

Background:

- Gout is one of the most common rheumatic diseases in adults and the prevalence has risen in many countries over the last few decades.
- A cardinal feature of gout is an elevated serum uric acid concentration defined as > 6.8 or 7.0mg/dL and is often due to either an increased uric acid production or decreased renal excretion.
- Allopurinol is a first line treatment option to maintain a serum urate level of < 6 mg/dL in chronic gout patients. Although generally well-tolerated, allopurinol has a rare but serious adverse event known as allopurinol hypersensitivity syndrome (AHS) characterized by exfoliative, urticarial, and purpuric lesions.
- Current guidelines recommend a gradual dose titration to a maintenance dose, exceeding 300 mg/day if necessary, to achieve a serum uric acid concentration of < 6 mg/dL, even for patients with renal impairment.
- Despite these facts, renal dose adjustments with allopurinol still occur in patients with chronic kidney disease (CKD).

Aim: To evaluate the appropriate use of allopurinol in patients with history of chronic kidney disease based on published literature, clinical studies, and analyses to determine therapeutic success and efficacy of renally adjusted allopurinol for the treatment of gout.

Approach

Methods: Randomized control trials, literature reviews, meta-analyses, and ongoing trials were searched using PubMed and Clinical Key, using the search terms “allopurinol”, “renal dosing adjustment”, “chronic kidney disease”, and “hypersensitivity syndrome”. The references of each identified article were evaluated for other applicable articles. Clinical trials assessing the effectiveness of renal dose adjustment of allopurinol in patients with CKD were included.

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Data

Results: Of the 27 sources that were found, 11 articles were relevant to the objective of this study and were included in this review.

Author + Year	Type of Article	Results
Dalbeth N, Stamp L (2007)	Literature Review	Further work is needed to clarify the safety and efficacy of allopurinol dose escalation, particularly in patients with renal impairment.
Lee H, Ariyasinghe J, Thirumoorthy T (2008)	Retrospective Study	Allopurinol hypersensitivity syndrome is a life-threatening cutaneous adverse reaction. Allopurinol should be initiated under clear indications with appropriate dosages. Potential associations with this syndrome include the Chinese race, the elderly, and patients with underlying renal impairment.
Gibson T, Rodgers V & Potter C (1982)	Retrospective Study	The renal function of patients given allopurinol did not change. Treatment with allopurinol resulted in a significant reduction of ammonium excretion, a phenomenon which could not be readily explained. Urate clearance also declined during allopurinol treatment, and the impaired urate clearance associated with gout became more evident. The most important observation was that allopurinol retarded an apparent decline of renal function.
Fuldeore M, Riedel A, Zarotsky V (2011)	Retrospective Study	About two out of every five patients with gout in this study population had CKD. Allopurinol doses were not adjusted in the majority of CKD patients. Serum uric acid control in gout was poor among patients without CKD and even worse among those with CKD.
Dalbeth N, Kumar S, Stamp L et al (2006)	Observational Study	For patients taking allopurinol, 70.9% were taking recommended doses, based on published allopurinol dosing guidelines. There were 4 patients (1.6%) with cutaneous hypersensitivity reactions to allopurinol, but none of these patients were taking higher than recommended allopurinol doses.
Goicoechea M, Garcia de Vinuesa S, Verdalles U et al (2010)	Randomized Control Trial	Allopurinol has shown to be beneficial in patients with CKD. It decreases CRP, slows down progression of disease and decreases hospitalization risk.
Vázquez-Mellado J, Morales E, Pacheco-Tena C (2001)	Retrospective Study	There was no increase seen in the prevalence of adverse reactions to allopurinol in patients who received higher allopurinol maintenance doses than those recommended according to creatinine clearance rate.
Thurston M, Phillips B, Bourg C (2013)	Literature Review	RCTs are needed to understand allopurinol dosing in patients with CKD. Current research and articles have limitations, including retrospective study design and small patient populations.
Stamp L, Taylor W, Jones P (2012)	Retrospective Case Control	AHS occurs more commonly in patients receiving higher starting doses of allopurinol. However, patients that tolerate this dose can be titrated up to achieve target serum urate level.
Stamp L, Chapman P, Barclay M et al (2017)	Retrospective Post Hoc Analysis	Allopurinol is effective at lowering urate levels even in those with severe CKD. This data indicates that allopurinol dose escalation to target serum urate is safe in patients with severe CKD.
Stamp L, O'Donnell J, Zhang M et al (2011)	Case-Control Study	Increasing doses of allopurinol above CrCl recommended dose showed a significant reduction in serum urate levels. No serious adverse events occurred. No AHS found. However, AHS usually takes 4-6 weeks to occur and these patients were stabilized on allopurinol for one month so risk of AHS development is low.

Conclusions: Further studies are needed to clarify the safety and efficacy of allopurinol dose adjustment for patients with altered renal function for treatment success. Additionally, there is lack of data in patients with AKI that receive allopurinol. Further studies should be done to evaluate the need for renal dose adjustment related to AKI. Current literature suggests that treatment failure of renally adjusted doses of allopurinol to control hyperuricemia may outweigh the risk of AHS development in patients with CKD. As such, the American College of Rheumatology gout guidelines recommends against renal dose adjustments of chronic allopurinol dosing in CKD.

Impact

Discussion: Out of the 11 articles that were reviewed, four concluded that allopurinol dose should be titrated up to therapeutic levels for CKD patients to ensure treatment success. Another three articles concluded that increasing doses of allopurinol do not significantly increase the risk of AHS. Another three articles found that further work needs to be completed to provide conclusive data. Alternatively, one article found that allopurinol dose should be adjusted based on renal function to ensure patient safety against AHS.

The unique feature about my innovation is advocating against the need for allopurinol dose adjustment in patients with CKD.

This solves the problem of improving patient outcomes for CKD patients receiving allopurinol for treatment of gout.