Title
Renal dosing of allopurinol results in suboptimal gout care

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We commend the authors of the '2016 updated EULAR evidence-based recommendations for the management of gout' for advocating starting allopurinol at a lower dose in patients with normal renal function.[1] Specifically, this recognises an approach to potentially decrease the risk of precipitating flares of gout early in the course of urate lowering, and also to possibly decrease the risk of severe cutaneous reactions (SCARs) compared with higher starting doses of allopurinol.[2] However, we note that the authors do not provide a recommendation on starting dose for patients with *renal impairment*, the patient group most likely to benefit from starting at a much lower dose of allopurinol.[2]

Furthermore, recommendation #9,[i] which advocates limiting the maximal dose of allopurinol based on creatinine clearance (CrCL), is concerning. It is well-documented that such practice results in suboptimal management of hyperuricaemia in the majority of patients with gout.[3] Adhering to the CrCL-based allopurinol dosing has been a major contributing factor to the under-treatment of gout since this scheme was published in 1984.[4] The authors acknowledge there are data to support careful dose escalation in those with renal impairment,[5 6] but then state that the low incidence of SCARs makes it difficult to quantify this risk and therefore advise against a dose-escalation approach. Allopurinol hypersensitivity syndrome/SCAR occurs early after starting allopurinol.[2 7] While renal impairment is a major risk factor for allopurinol hypersensitivity syndrome/SCAR, there is no evidence that long-term restriction of allopurinol dose according to CrCL lowers this risk in patients who tolerate low starting doses of allopurinol.[8 9] The approach advocated by the European League Against Rheumatism panel could lead to a clinical situation where patients may be exposed to potential risks of allopurinol, without the benefits achieved by careful dose escalation to achieve serum urate target. By focusing on the maximum dose of allopurinol rather than the starting dose in patients with renal dysfunction, an important safety point has been missed and this may inadvertently reinforce fears of prior decades about allopurinol use in patients with renal dysfunction where more recent data[5] has shown that allopurinol can be safely used in patients with renal impairment.

Recommendation #9 is also likely to reduce the quality of care for the many people with gout in regions with limited access to urate-lowering therapies other than allopurinol. Furthermore, recommending febuxostat if renally dosed allopurinol is insufficient for gout management raises potential concern for patients with renal impairment. Studies examining the safety and efficacy of febuxostat in people with gout and comorbid renal impairment have been sparse, with 266 subjects with chronic kidney disease (CKD) stage 3 randomised to febuxostat in the CONFIRMS clinical trial,[10] and only 19 subjects with CKD stage 4 randomised to febuxostat in another recent trial.[11] This is important, as febuxostat itself has been associated with SCARs, including in patients with renal impairment and/or previous hypersensitivity to allopurinol, leading the European Medical Agency and Health Canada to issue warnings regarding this issue.[12 13] It is presently not known if this represents a true cross-reactivity or rather an individual's propensity to experiencing a drug reaction.

The lack of clarity in the optimal management of hyperuricaemia in patients with gout and renal impairment should have also been considered an important topic for future research. Given that almost half of all people with gout suffer from moderate-to-severe CKD and the limited treatment options available in this setting, a major knowledge gap and unmet need remains the optimal means of managing these challenging presentations. We recognise that a large, well-designed study will likely be needed, considering the low incidence of allopurinol hypersensitivity syndrome (AHS)/SCAR reactions. Nonetheless, recommending dosing of allopurinol based on CrCL in the absence of evidence to support this practice will not improve the historically poor management of gout in patients with renal disease.

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[i]Recommendation #9: "In patients with renal impairment, the allopurinol maximum dosage should be adjusted to creatinine clearance. If the SUA target cannot be achieved at this dose, the patient should be switched to febuxostat or given benzbromarone with or without allopurinol, except in patients with estimated glomerular filtration rate <30 mL/min."

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