

**ALLOPURINOL: A NECESSARY EVIL**

Dear Sir,

We read with interest the article by Lee et al with reference to their experience in caring for 28 patients with allopurinol drug-induced hypersensitivity syndrome (DHS) with a mortality rate of 18%.<sup>(1)</sup> We thank them for highlighting DHS, which is a major concern to physicians. By virtue of it being a case series, the denominator, which is the number of patients prescribed allopurinol in Singapore, is not available. In the majority of patients, allopurinol is well tolerated. Approximately 2% of patients develop a mild rash. The true incidence of DHS is unknown, although it is estimated to be about 0.1%.

While we wholeheartedly agree with the authors' comments that allopurinol therapy is not without its risks and that consideration of the risk-benefit ratio is imperative, we wish to clarify some issues. The first recommendation based on their findings stated that allopurinol should be initiated with clear indications; asymptomatic hyperuricaemia and non-specific joint pain, which made up a third of their patient pool, was being treated with allopurinol. This raises the issue of diagnostic difficulty, and can only be addressed via continuing medical education and the accessibility (to the point of contact physician) of a practitioner well versed in the treatment of gout.

The second recommendation was to screen carefully for the need for allopurinol, in particular at-risk groups of DHS, such as the elderly, Chinese race and patients with underlying renal disease. Although it is prudent to be wary of DHS in these groups, nevertheless, they should not be in the exclusion criteria for allopurinol therapy in view of the significant derangement of quality of life due to chronic tophaceous gout with its comorbidities, ranging from diabetes mellitus, metabolic syndrome to coronary artery disease.

The third recommendation stated that allopurinol dosage should be corrected according to the creatinine clearance. Allopurinol dosing in patients with chronic kidney disease (CKD) lacks consensus. The United States Food and Drug Administration dosing guidelines for allopurinol due to renal dysfunction are incomplete, as they recommend limiting the maximum allopurinol dose to 200 mg/day with creatinine clearance test [CCT] 10-20 ml/min, and to 100 mg/day in CCT <10 ml/min, without specifying a scale for dosing allopurinol in moderate CKD.<sup>(2)</sup>

The nephrology-based allopurinol maintenance dosing guidelines of Hande et al,<sup>(3)</sup> quoted by Lee et al<sup>(1)</sup> and ingrained in most practitioners and pharmacists, was proposed to reduce the risk of serious adverse reactions related to allopurinol without reducing its efficacy. It originated after a literature review of case reports showed that most patients with DHS had renal insufficiency, and received standard allopurinol doses (300 mg/day) with the assumption that higher serum oxypurinol levels were linked to DHS. A significant number of patients were on thiazide diuretics, which are known to interfere with the excretion of oxypurinol. Severe DHS is not dose dependent and does not correlate with oxypurinol levels.<sup>(4)</sup> There is no evidence that a systematic dose reduction in renal disease attenuates DHS risk.<sup>(5,6)</sup> These guidelines may be most suitable as the starting dose in an individual patient, as suggested by the recently-published quality-of-care indicators for gout.<sup>(7)</sup> In recent years, there has been a growing recognition that the intensive lowering of serum uric acid (SUA) to a target of 6 mg/dL (360 µmol/L) is required to achieve suppression of acute gout flares and regression of tophi.<sup>(8,9)</sup>

The optimal allopurinol dosing regimen remains uncertain but it is clear that the target of urate lowering therapy should be a SUA level of 6 mg/dL. Therefore, initiation of allopurinol should be at a low dose (typically 50–100 mg daily) with a gradual dose escalation to a maintenance dose that achieves a SUA 6 mg/dL, and with due care and consideration given, if the dose is increased beyond that suggested by the guidelines, this should be individualised for patients with gout and moderate to severe CKD (CCT < 60 ml/min). This approach requires close monitoring of SUA concentrations, and a careful analysis of the risks and benefits. For example, given the very small risk of severe adverse drug reactions in patients taking allopurinol, the calculated risk of persistent hyperuricaemia may be greater than the risk of allopurinol-related adverse events, especially for patients with severe gout. A gradual introduction of allopurinol is recommended for all patients with gout, as initiation of full-dose allopurinol may lead to a rapid decline in SUA, with precipitation of an acute gout flare.

The fourth recommendation advised that patients should be monitored during the first two months for possible DHS. We would caution that vigilance is required, not only within the first few months of therapy with monitoring

of the liver panel, chemistry profile and full blood count, but also with progressive dose increments of allopurinol, in view of the potential for myelosuppression and hepatotoxicity.

The final recommendation was that patients and doctors should be educated on the early recognition, and prompt withdrawal of allopurinol, in the event of DHS. Explicit advice has to be given to discontinue the drug and contact the prescriber at the first sign of rash, painful urination, blood in the urine, irritation of the eyes, or swelling of the lips/mouth. Until febuxostat is available in Singapore, allopurinol will continue to be the mainstay of effective urate-lowering therapy. In conclusion, the fear of DHS with allopurinol is not unfounded, but should be tempered by the reality that it is a necessary "evil".

Yours sincerely,

Anita YN Lim

Gim Gee Teng

Division of Rheumatology  
 Department of Medicine  
 National University Health System  
 5 Lower Kent Ridge Road  
 Singapore 119074  
 Email: anita\_lim@nuhs.edu.sg

## REFERENCES

1. Lee HY, Ariyasinghe JT, Thirumoorthy T. Allopurinol hypersensitivity syndrome: a preventable severe cutaneous adverse reaction? *Singapore Med J* 2008; 49:384-7.
2. US National Library of Medicine DailyMed: FDA information: allopurinol tablet. Available at: [dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5047](http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5047). Accessed September 14, 2009.
3. Hande KR, Noone RM, Stone WJ. Severe allopurinol toxicity. Description and guidelines for prevention in patients with renal insufficiency. *Am J Med* 1984; 76:47-56.
4. Puig JG, Casas EA, Ramos TH, Michan AA, Mateos FA. Plasma oxypurinol concentration in a patient with allopurinol hypersensitivity. *J Rheumatol* 1989; 16:842-4.
5. Dalbeth N, Kumar S, Stamp L, Gow P. Dose adjustment of allopurinol according to creatinine clearance does not provide adequate control of hyperuricemia in patients with gout. *J Rheumatol* 2006; 33:1646-50.
6. Dalbeth N, Stamp L. Allopurinol dosing in renal impairment: walking the tightrope between adequate urate lowering and adverse events. *Semin Dial* 2007; 20:391-5.
7. Mikuls TR, MacLean CH, Olivieri J, et al. Quality of care indicators for gout management. *Arthritis Rheum* 2004; 50:937-43.
8. Perez-Ruiz F, Calabozo M, Pijoan JL, Herrero-Beites AM, Ruibal A. Effect of urate-lowering therapy on the velocity of size reduction of tophi in chronic gout. *Arthritis Rheum* 2002; 47:356-60.
9. Shoji A, Yamanaka H, Kamatani N. A retrospective study of the relationship between serum urate level and recurrent attacks of gouty arthritis: evidence for reduction of recurrent gouty arthritis with antihyperuricemic therapy. *Arthritis Rheum* 2004; 51:321-5.