Therapeutic advances in the management of gout have renewed interest in the treatment of this common, painful condition. Compliance with European League Against Rheumatism (EULAR) treatment recommendations is poor, with lifestyle advice infrequently offered by doctors or implemented by patients [1]. Inadequate control of hyperuricaemia in gout may lead to chronic tophaceous disease, worsening of joint erosion, absenteeism from work and reduced productivity [2].

The primary option for long-term urate-lowering therapy is allopurinol. While investigating the anti-neoplastic properties of 6 mercaptopurine (6-MP) in the 1950s, Gertrude B. Elion and George H. Hitchings discovered that xanthine oxidase generated thiouric acid as a metabolite of 6-MP. A short time later allopurinol was developed, approved by the United States Food and Drug Administration (FDA) in 1986 and resulted in a Nobel Prize award for the researchers [3].

Allopurinol remains an extremely effective prophylactic agent against gouty flares, with a simple once-daily dosing regimen, yet only 30–60% of patients with gout are still prescribed allopurinol a year after initiation of therapy [4]. So why do surprisingly few patients continue using this drug? The risk of hypersensitivity can limit its use [5]. Minor self-limiting drug reactions are relatively common, which is estimated in up to 10% of patients, and include itching, rash and gastrointestinal problems [5]. A well-described desensitization programme successfully allows >70% of patients who have developed simple cutaneous reactions to continue taking allopurinol, although sometimes late adjustment of the dose may be required [6]. The more serious, indeed potentially fatal, allopurinol hypersensitivity syndrome (AHS) is far less common, estimated at 0.4% of patients. It occurs 2–6 weeks after treatment is started, with features such as eosinophilia, liver and renal dysfunction, vasculitis, bone marrow suppression and rash [7]. In such situations, allopurinol should never be reintroduced.

Known risk factors for developing AHS include renal impairment, older age, comorbidities, diuretic use of thiourea and a genetic predisposition [8, 9]. For instance, genetic predisposition has been observed in Han Chinese associated with HLA-B allele B*5801, and has an odds ratio exceeding that reported for HLA-B27 and AS [9]. The prospect of haplotype testing in targeted patients to further assess the risk of AHS may soon become a clinical reality. Currently, however, clinicians may reduce the risk of AHS by initiating allopurinol dose according to creatinine clearance in patients who are suitable to receive therapy [10]. Indeed, if appropriate doses, based on creatinine clearance, are used, then AHS is seldom seen [5]. Moreover, although hypersensitivity is often stated as a reason for discontinuing allopurinol, ~95% of patients are able to tolerate the drug [11]. We must ensure that we have not failed to treat, before we label patients as having treatment failure gout. Optimal management should include encouraging compliance and titrating the allopurinol dose to avoid undertreatment.

Escalating allopurinol therapy to be effective is safe, but often not achieved [1]. Recent guidelines have recommended the control of serum urate in the range of 30–36 μmol/l for patients with gout [12, 13]. However, guidelines are of limited use if they are not accessed. Most patients with gout are treated in general practice and never enter the domain of the rheumatologist, and general practitioners (GPs) are unlikely to read guidelines that are published in rheumatology journals or present on rheumatology websites. A concerted effort is needed to better disseminate and increase awareness of algorithms for gout in the primary-care setting.

So why is it that so many practitioners are unfamiliar with allopurinol use, and either fail to initiate or titrate to an effective dose despite the recent development of both British Society of Rheumatology and EULAR guidelines [12, 13]? In part, the answer may simply be that physicians tend not to follow clinical practice guidelines, with the main barriers to changing behaviour being either lack of awareness of the guidelines or unfamiliarity with the content [14]. In a seminal sociological dissection of the medical profession, Friedson identified five traits of the typical clinician that helped explain the disconnection between guidelines and clinical practice [15]. One trait was that physicians depend more on personal judgement than empirical evidence. Optimizing clinical judgement may, therefore, be a more fruitful priority of education in gout management and rheumatologists should enthusiastically be taking the initiative as outlined in an editorial [16]. Moreover, doctors who embrace and follow the guidelines, while optimizing allopurinol therapy, may find that only a small cohort of patients will require the newer therapeutic agents, of which the safety profiles remain far less clear [7].

Finally, rheumatologists should consider advising their GP colleagues of the appropriate dose titration for each patient and any necessity for blood monitoring of urate, particularly if they do not offer secondary care follow-up. Gout would be ideal for inclusion in the Quality and Outcomes Framework in the UK given its prevalence,
chronicity, a cheap intervention (allopurinol) and simple blood monitoring of uric acid levels. Contrary to a review [7], the answer to addressing the disparity in management of gout between non-specialists and specialists is not to refer more patients to secondary care, but to do triage referral for those with comorbidities, genuine intolerance to allopurinol and ongoing flares despite compliance.

After decades of limited options, new drugs for managing gout are a welcome development. However, allopurinol dose titration (with desensitization if necessary), encouraging compliance, and educating both doctors and patients by wider dissemination of guidelines, will largely achieve this in most patients.

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