Response: Renal dosing of allopurinol results in suboptimal gout care by T Neogi *et al*

We sincerely appreciate the interest shown by Dr T Neogi and colleagues[1] concerning our 2016 revised European League Against Rheumatism (EULAR) recommendations for the management of gout.[2]

Dr T Neogi and colleagues raised concern with the ninth item, in which we recommend to adjust the maximum dosage of allopurinol according to the creatinine clearance (CrCl) in order to decrease the risk of severe cutaneous allergic reactions (SCARs).

First, we would like to emphasise that these recommendations were written from a European perspective. In many countries in Europe, regulatory agencies require this adjustment, an important point we took into account for the elaboration of this recommendation. Furthermore, in addition to rheumatologists, the task force included general practitioners, who manage the vast majority of people with gout, patients with gout who are on urate-lowering treatment, and evidence-based medicine (EBM) experts. Therefore, the recommendations reflect perspectives from multiple stakeholders and follow the principles of EBM by examining all types of evidence (patient views, expert opinion and experience, research evidence) in the realisation that each has its strengths and weaknesses, and it is only when all align that we get close to 'accepted best practice'.

Second, assessing the benefits and the risks of administering allopurinol to patients with chronic kidney disease (CKD) is difficult. The literature that addresses the safety of allopurinol use in patients with CKD is predominantly retrospective. After an extensive literature review, we concluded that the level of evidence to support that a dose escalation strategy is safe in patients with CKD is low. For instance, in the quoted paper by Lisa Stamp,[3] the authors examined the effects of increasing the dosage of allopurinol above the recommended dose based on the CrCl. Safety was analysed on the basis of just 45 patients, and given that the incidence of allopurinol-induced SCARs is about 0.7/1000 patient-years in allopurinol initiators,[4] one can easily conclude that this study was insufficiently powered to draw any firm conclusion. Furthermore, it is important to note that patients enrolled in this study had been tolerating CrCl-based doses of allopurinol for at least a month prior to titration, because it is known that the risk of SCARs occurrence is more common in the weeks following initiation.[5]

Third, as mentioned by Dr T Neogi, it is true that we lack clear evidence that restriction of allopurinol maintenance dose in patients with CKD might decrease the risk of SCARs. It would be wise also to remind that we also lack evidence that a starting dose of 1.5 mg per unit of estimated glomerular filtration rate (eGFR) (mL/min/1.73 m^2) might reduce the occurrence of SCARs. Of note, the sole prospective case–control study,[6] not cited by T Neogi, clearly showed that renal failure was significantly associated with the delayed clearance of plasma oxypurinol, which might have antigenic properties to stimulate cytotoxic T lymphocytes.[6] Moreover, in this study, renal failure increased the risk of SCARs and was correlated with a poor prognosis, in particular mortality. In addition, the starting dose, found to be associated with SCARs in a retrospective study,[7] was not associated in this prospective study with an increased risk of severe allergic reactions. Finally, in subjects with severe renal impairment (eGFR <30 mL/min/1.73 m^2), there was no significant difference in the values of initial dose/eGFR between allopurinol-SCAR and tolerant controls, contrary to what was found previously.[7]

Therefore, there remains uncertainty surrounding the risk/benefit ratio of allopurinol in patients with CKD, and it is unlikely that we will have prospective longitudinal data to allow determination of the appropriate starting dose and whether we can or cannot safely increase the dose in patients with CKD. We discussed in depth this issue with patients who were part of the task force, and all of them agreed, as did the general practitioners, that we should apply a precautionary principle. Thus, we recommend to initiate allopurinol with a maximum starting dose of 100 mg daily and to keep a conservative approach for the maintenance dose to be adapted to the CrCl, as did the British Society of Rheumatology[8] and the last EULAR recommendation.[9]

Fourth, we disagree that this recommendation will impair the quality of care for patients with CKD. On the contrary, we strongly believe that this will facilitate the management of hyperuricaemia in these difficult-to-treat patients. As shown in figure 2, we recommend that if the allowed allopurinol dosage does not achieve the predefined urate target levels (5 or 6 mg/dL), a switch to febuxostat or a combination therapy with an old or recent uricosuric[10] should be undertaken. Recent findings indicate that febuxostat remains safe and effective in patients with eGFRs as low as 15 mL/min,[11 12] and that there is no cross-reactivity between febuxostat and allopurinol.[13] Thus, advocating that limiting the allopurinol dosage in patients with CKD will result in suboptimal management is incorrect, because there are now alternatives to consider—this negative assumption is based on a study published in 2006,[14] well before the availability of febuxostat and the novel uricosuric lesinurad.[10]

To conclude, we believe that initiating patients with CKD with a maximum of 100 mg allopurinol daily, adapting the maintenance dose to the CrCl and offering therapeutic alternatives, if necessary, such as febuxostat or a combination of allopurinol and a uricosuric, should both decrease the risk and severity of SCARs and increase the quality of care.

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