Response to: 'Cutaneous adverse events with febuxostat after previous reactions to allopurinol: comment on the artcile by Singh and Clevland' by Quills *et al*

We appreciate the interest and comments by Quilis *et al*[1] on our recent publication.[2] Quilis *et al* draw our attention to the incidence of cutaneous adverse reactions (CARs) with febuxostat in people who had already had reactions with allopurinol. In their study which included several practices in Spain from 2011 to 2018, 15% of people developed these reactions with febuxostat[1] compared with the 9%–15% range reported previously for similar patient populations from the USA and France.[3 4] CARs are frequent, and are associated with significant morbidity.[5] Interestingly, the rate of CARs in people newly starting febuxostat and not previously exposed to allopurinol was 2.5% in the French study,[4] similar to the rate of 31 per 1000 patient-years in our study.[2] So why is the risk of CARs with febuxostat increased by four-fold to six-fold (2.5% to 9%–15%) in people with previous allopurinol-associated CARs compared with lower rate in the general population? Does allopurinol hypersensitivity increase the risk of hypersensitivity reactions to another urate-lowering therapy? Is there some cross-reactivity,[6] despite some differences in the mechanism of action between these two medications? Are some allopurinol-associated CARs just adverse events and not hypersensitivity reactions that usually manifest as severe CARs (SCARs)[7 8]? These are important questions to answer.

Allopurinol-associated CARs and SCARs are uncommon adverse events, and intriguing from research perspective. Given the unpredictability in occurrence and a fatal outcome in some cases, ULT-associated CARs/SCARs are important clinically. Future studies need to examine this clinical problem using various innovative approaches. Systematic studies of gene–environment–comorbidity–medication interactions are needed to solve this puzzle.

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