Allopurinol versus febuxostat hypersensitivity reactions in the US elderly: differences in study outcomes and populations. Response to: 'Correspondence to "Hypersensitivity reactions with allopurinol and febuxostat: a study using the Medicare claims data" by Ma *et al*

We appreciate the interest and comments by Dr Ma and colleagues¹ on our recent publication.² Not surprisingly, our study results differ from their previous study.³ We agree with their point regarding the differences in the definition of the main study outcome and the International Classification of Diseases (ICD) codes used to define them and discussed it in our paper.² We examined the incidence of hypersensitivity reactions using two previously published validated algorithms by Strom *et al* and Wright *et al* compared with their ICD algorithms to define cutaneous hypersensitivity reactions;³ we are unable to locate the accuracy statistics of their algorithms in this publication. Differences in study findings with regard to the risk of these adverse outcomes with allopurinol and febuxostat indicate that in future studies, both types of definitions (ours and theirs) need to be examined simultaneously. This would make the study results robust and allow a more definitive answer to the question: is the risk of all hypersensitivity reactions, or all cutaneous hypersensitivity reactions, or severe cutaneous hypersensitivity reactions, different for allopurinol-exposed versus febuxostat-exposed populations?

We respectfully disagree with their comment that allopurinol-associated hypersensitivity reactions would have been attributed to febuxostat in error, since patients likely started febuxostat after stopping allopurinol. We required a >30-day period between prescription fills, for the definition of a new allopurinol (or febuxostat or colchicine) prescription start to avoid the issue of misattribution. This 30-day period also accounted for any residual biological effects of medications. Misclassification is always possible; however, we likely minimised it with the use of this approach.

We agree that a lot of patients may be concurrently using non-steroidal anti-inflammatory drugs (NSAIDs), which are known to be associated with hypersensitivity reactions. This could have confounded findings from all epidemiological studies to-date including our study, since most NSAIDs are available over-the-counter in most countries and could not be accounted for in any study so far. The hypersensitivity reactions seen with colchicine in our study might indicate the concomitant use of other medications (NSAIDs) not captured in our analyses; they are equally likely to be due to concomitant use of medications used for other disorders (cardiovascular disease, infections; ACE inhibitors, antibiotics, antivirals, anticonvulsants),^{4,5} subclinical undiagnosed chronic conditions (not captured in Deyo-Charlson comorbidity index), drug-drug interactions and drug-disease interactions⁶ that are very common in the elderly. Importantly, we are reporting associations, not causality. Establishing causality is difficult with observational studies.

We discuss and agree that the incidence of (and susceptibility to) hypersensitivity reactions likely varies by the country setting,² related to differences in the HLA-B*5801 allele frequencies. Analysis of severity of hypersensitivity reactions was not a study objective. Standardised documentation using scoring systems as they note in their letter can also allow for a better understanding

of these outcomes in the future. The almost universal use of electronic health records should make this possible in the future.

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