Confounding by indication and ethnicity difference? Comment on 'Hypersensitivity reactions with allopurinol and febuxostat: a study using the Medicare claims data'

We read with great interest the study by Singh and Cleveland[1] that investigated the risk of hypersensitivity reactions (HRs) with allopurinol and febuxostat using Medicare claims data. These authors analysed a national cohort in the 5% Medicare beneficiary sample randomised from 2006 to 2012 of adults older than 65 years who experienced a new treatment episode with allopurinol, febuxostat or colchicine. They reported the following incidence rates for HRs: allopurinol, 23.9; febuxostat, 30.5; and colchicine, 25.7 cases per 1000 person-years. Combination treatments of febuxostat+colchicine, allopurinol+colchicine and febuxostat+colchicine+allopurinol increased the incidence of HRs to 56.8, 27.4 and 89.1 per 1000 person-years, respectively. Based on a propensity-matched analyses of allopurinol versus febuxostat (5:1), which showed febuxostat with an HR of 1.25 (95% CI 0.93 to −1.67), the study concluded there was no difference between the HRs for allopurinol versus febuxostat. However, some study results and aspects of these findings must be clarified.

First, Lin *et al*[2] reported a higher incidence rate of HRs with allopurinol versus febuxostat (15.37 vs 3.48 per 1000 person-years, respectively), which differs from the conclusion reached by Singh *et al*. In clinical practice, physicians are generally concerned about the potential adverse effects of allopurinol, such as Steven-Johnson syndrome for their older adult patients or those who have chronic kidney disease, leading them to choose febuxostat versus allopurinol. This choice may cause an overestimation of the rate of HRs with febuxostat and even doubts of confounding by indication.

Regarding ethnicity, Lu *et al*[3] found that white patients have lower frequencies of human leucocyte antigen-B*5801 in the USA compared with Asian patients, which correlates with a lower risk for Stevens-Johnson syndrome in white patients and may result in the study showing a lower incidence of HRs in a predominantly white population.

Another key issue for the study by Singh *et al* is that several numeric discrepancies appear in the text versus the abstract. For example, the abstract stated the crude incidence rates of HRs by drug as follows: allopurinol, 23.7; febuxostat, 30.7; and colchicine, 25.6 cases per 1000 person-years. However, the Results section and table 2 in the text by Singh *et al*, these values are listed as 23.9, 30.5 and 25.7, respectively.

Finally, the discussion about the safety of allopurinol, febuxostat and colchicine is an important issue that must be addressed by further research.

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