Correspondence to 'Hypersensitivity reactions with allopurinol and febuxostat: a study using the Medicare claims data'

We read with great interest the article by Singh and Cleveland, which the authors reported that the observed hypersensitivity reactions (HSRs) associated with allopurinol and febuxostat were not different.¹ This conclusion differs from previous studies on HSRs associated with allopurinol and febuxostat using claimed data² and intramural databases.³ The discrepancy may arise from different inclusion criteria for the diagnosis of HSRs based on International Classification of Diseases, Ninth Revision (ICD-9) coding system, methods for identifying causative drugs, methods for stratification, as well as ethnicity of the involved population.

The definition of HSR in the study by Singh and Cleveland adopted ICD-9 diagnostic codes specifying eosinophilia (288.3), HSR-associated arthropathy (713.6), anaphylactic reactions (995.0) or unspecified adverse drug effect (995.2) or allergy (995.3), plus the baseline exclusion for E930 to E949.¹ On the contrary, in our previous studies, the definition of cutaneous adverse reactions (CARs) using the Taiwanese registry database involved drug-induced dermatitis (693.0), erythema multiforme (695.1) or erythematous conditions (695.89 or 695.9).²⁻⁴ Likewise, another study based on intramural database and meta-analysis defining severe CARs as 693, 695.1 or 695.9/695.89 also suggested that the overall incidence of febuxostat-associated HSR was lower than that of allopurinol (0.2 vs 2.7 per 1000 users; $p < 0.001$), with regard to these dermatological manifestations.³ From a clinical standpoint, as allopurinol-associated HSRs or CARs are delayed type of hypersensitivity, which normally involve the onset of maculopapular eruption, drug reactions with eosinophilia and systemic symptoms, or Stevens-Johnson syndrome/toxic epidermal necrolysis,^{5,6} defining HSR with ICD-9 codes 713.6, 995.0 or 995.2, should be not appropriate. This suggests that the discrepancy between these studies could be attributed to the inclusion criteria for the diagnosis of HSRs.

Previous studies have pointed out that colchicine rarely causes HSR, as its notoriety score in the algorithm of drug causality for epidermal necrolysis (ALDEN) is zero⁷; the main reason of colchicine being reported as HSR-associated drugs would be due to the fact that it is oftenly used in conjunction with allopurinol.⁸ Likewise, without further algorithms to confirm drug causality among these ICD-9 coding-based analyses,^{1,2} patients with allopurinol-associated HSRs who have been shifted to febuxostat treatment would also lead to the conclusion of febuxostat being counted as the culprit drug. Apart from HSR-inducing gout or hyperuricaemia medications such as allopurinol and febuxostat,¹⁻³ frequently prescribed drugs like non-steroidal anti-inflammatory drugs (NSAIDs) are commonly involved in HSR as well.⁹ As NSAIDs are widely used and are available over the counter, most of these epidemiological studies on HSR could not rule out concurrent use of these causative drugs. Without reflective parametrics for instance, chronology, ALDEN⁷ or Narenjo score with weight of notoriety,¹⁰ studies based on ICD-9 coding system may not identify the specific causative drug among multiple used drugs. Thus, it may be hard to distinguish the most likely causative medications when considering all the taken drugs as allergens.

Although allopurinol-associated HSR has been suggested to be dose dependent,^{11,12} the underlying mechanisms of febuxostat and colchicine-associated HSRs remain unclear. While Singh and

Cleveland stratified the patients with drug dose cut-offs,¹ the severity of incident HSRs were not analysed. On the contrary, the other studies either stratified for respective HSR severity but adopted different codes for HSR definition,² or used intramural databases without stratifying the doses of the associated drugs.³ Specifically, the conclusion that allopurinol was associated with higher risks of CARs than febuxostat in one of these studies was based on the stratification of severity.² This suggests that the stratification methods may attribute to the observed discrepancies.

Furthermore, the incidence rate of HSR varies among countries. For instance, the incidence rates of HSRs in the USA were estimated to be 23.7 for allopurinol, 30.7 for febuxostat and 25.6 for colchicine, per 1000 person years¹; whereas in Taiwan, the annual incidence rates were 4.68 per 1000 new allopurinol users for HSR, 2.02 per 1000 new allopurinol users for HSR-caused hospitalisation and 0.39 per 1000 new allopurinol users for HSR-caused mortality, as stratified by severity.⁴

Particularly, the prevalence of HLA-B*58:01 allele, an allopurinol HSR-associated gene, fluctuates among countries¹³; moreover, the association of HLA-B*58:01 with allopurinol-induced HSR varies among populations.¹⁴ It is possible that the susceptibility to febuxostat and colchicine-associated HSRs differs among ethnicities as well.

For the above reasons, we recommend that the cooperation of bedside diagnostics and laboratory is necessary to discriminate which of the causative drugs induce each hypersensitivity event, as confirmed with algorithms involving chronology, ALDEN or Narenjo score with weight of notoriety score, to compare their incident HSRs.

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