

Correspondence

Accurate phenotyping of cross-reactive hypersensitivity is essential to shed light on the underlying mechanisms in NSAID-induced urticaria/angioedema

To the Editor:

The article "Distinct transcriptomic and metabolomic profiles characterize NSAID-induced urticaria/angioedema patients undergoing aspirin desensitization" by Tay et al¹ in *The Journal of Allergy and Clinical Immunology* tries to characterize transcriptomic and metabolomic profiles in patients with nonsteroidal anti-inflammatory drug (NSAID)-induced urticaria/angioedema (NIUA) who are undergoing aspirin desensitization. Patients were included exclusively on the basis of clinical history, without an aspirin drug provocation test (DPT). We would like to comment on both patient selection and transcriptomic analysis.

Concerning the patients, 7 of 10 reported only 1 reaction (4 to aspirin and 3 to other NSAIDs). As only 1 reaction occurred, it would not be possible to declare that the patients developed cross-reactive hypersensitivity reactions (CRHRs). To consider a potential CRHR, patients must experience at least 2 reactions to 2 or more unrelated strong COX-1 inhibitors.^{2,3} Nevertheless, this condition was not met in the study by Tay et al.¹ The remaining patients (apparently 3) reported 2 to 4 reactions (1 to aspirin and 3 to other NSAIDs); however, neither the exact number nor the specific culprit were specified. If only clinical history is taken into account, diagnosis may be ruled out in around 24% of patients in whom NIUA is suspected.⁴ Indeed, confirmation is achieved in only 63% of patients reporting 2 reactions.

Tay et al¹ stated that NSAID DPTs need to be interpreted carefully. We do not agree with this statement. Oral aspirin DPT is the criterion standard to confirm CRHRs, particularly in cases involving nonsevere reactions such as NIUA, and the potential confounding factors mentioned (viral infection, physical activity) are easily controllable. Tay et al¹ explained that their patients did not undergo a high-dose aspirin DPT on account of the cardiovascular risk. However, as NIUA involves only skin and no other organs, DPTs are safe even at high doses. Thus, the risk-benefit balance may not be a contraindication for a DPT. Additionally, in these patients, NIUA lasted a median of 9 years. We have demonstrated that 60% of patients with NIUA develop NSAID tolerance over time (median time 5 years).⁵ Therefore, aspirin DPT is required for diagnosis of NIUA, as many patients may no longer be hypersensitive.

Finally, the aspirin doses commonly used as antiplatelets (100 mg) are usually tolerated by patients with NIUA, and if a reaction

occurs, it induces only mild cutaneous symptoms. Consequently, whether desensitization is really needed should be evaluated.

Regarding transcriptomics, doubts arise about the lack of explanation for the use of 2 different annotations to generate gene-level counts and a radial 2-dimensional plot instead of volcano or radial 3-dimensional plots (including *P* values), as well as about the absence of tables with full differential expression analysis and functional enrichment. Furthermore, a principal component analysis plot displays 3 overlapping confidence ellipses, showing no separation between the 3 groups considered. In addition to issues related to patient selection, this might also suggest a bias affecting some unaddressed variables (age, sex, and ethnicity, among others). Consequently, the differential expression results found may arise not really from NIUA but rather from undeclared variables. Finally, the primary objective of the study by Tay et al¹ was to characterize patients with NIUA who are undergoing aspirin desensitization profiles; however, no differences before and after this procedure seem to have been found.

Taken together, our comments about the study by Tay et al¹ aim to raise various concerns not only about patient selection and transcriptomic analysis but also about the potential findings.

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