Is anti-TPO IgG and total IgE clinically useful for the detection of autoimmune chronic spontaneous urticaria?

To the Editor:

Recently, Kolkhir et al[1] published an interesting study regarding how high anti– thyroid peroxidase (aTPO) immunoglobulin G (IgG) and low total IgE combined ($aTPO^{high}/IgE^{low}$) are linked to features of type IIb autoimmune chronic spontaneous urticaria (aiCSU). In the study's conclusion, they highlight that $aTPO^{high}/IgE^{low}$ is a useful diagnostic marker for identifying patients with aiCSU in clinical practice. These results are in line with the current recommendation given by the European Urticaria guidelines.[2] Also, they define the presence of aiCSU based on 4 indirect markers, mainly the basophil activation test (BAT) as the best single marker.

We believe that the study generates interesting findings for a better understanding of the pathogenesis of urticaria, but because a statistical difference does not always translate into a clinically relevant difference, we have some doubts regarding its possible clinical utility. To use diagnostic tests in clinical practice, it is necessary to validate their diagnostic accuracy.

Based on the data provided in the article, from 43 patients who had $aTPO^{high}/IgE^{low}$, 19 of them had a positive BAT result. Among patients without $aTPO^{high}/IgE^{low}$, 43 of 344 had a positive BAT result. Evaluating the diagnostic accuracy (Figure 1), we observed that the test's sensitivity and positive predictive value are low; only 1 of each 3 patients with positive BAT was detected with this test combination. The specificity and negative predictive value of the test are high but this is due to the low prevalence of positive BAT (16%); therefore, 2 out of 3 patients with positive BAT would be erroneously classified as without aiCSU according to the combined test of aTPO IgG and total IgE.

In addition, the use of BAT with basophils from patients and serum from a control subject indicates autoreactivity but does not allow defining the mechanism that leads to basophil activation; it could be mediated for example by IgE, IgG, or IgM.[3-5] So patients with positive BAT have autoreactivity but we cannot ascertain that it is type IIb autoimmunity.

In conclusion, we believe that it is necessary to evaluate the accuracy of biomarkers that have been identified in urticaria because, although many may be promising for clinical utility, they are not always reliable.

Jorge Sanchez, MD, MS, PhD
Juan Felipe Lopez, MD, MS
Leidy Alvarez, MD, MS

Group of Clinical and Experimental Allergy, IPSU Clinic, University of Antioquia, Medellín, Colombia.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.
Received for publication January 30, 2022; accepted for publication February 22, 2022.

Corresponding author: Jorge Sánchez Caraballo, MD, MS, PhD, Group of Clínical and Experimental Allergy, IPS-U clinic University of Antioquia, Cra 27 #37 B sur 69, Envigado, Colombia. E-mail: jorgem.sanchez@udea.edu.co.

REFERENCES

1. Kolkhir P, Kovalkova E, Chernov A, Danilycheva I, Krause K, Sauer M, et al. Autoimmune Chronic Spontaneous Urticaria Detection with IgG Anti-TPO and Total IgE. J Allergy Clin Immunol Pract 2021;9:4138-46.e8.
2. Zuberbier T, Abdul Latiff AH, Abuzakouk M, Aquilina S, Asero R, Baker D, et al. The international EAACI/GA^{2}LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. Allergy 2022;77:734-66.
3. Asero R, Marzano AV, Ferrucci S, Lorini M, Carbonelli V, Cugno M. Co-occurrence of IgE and IgG autoantibodies in patients with chronic spontaneous urticaria. Clin Exp Immunol 2020;200:242-9.
4. Sánchez J, Sánchez A, Cardona R. Causal relationship between anti-TPO IgE and chronic urticaria by *in vitro* and *in vivo* tests. Allergy Asthma Immunol Res 2019;11:29-42.
5. Maurer M, Altrichter S, Schmetzer O, Scheffel J, Church MK, Metz M. Immunoglobulin E-mediated autoimmunity. Front Immunol 2018;9:689.

https://doi.org/10.1016/j.jaip.2022.02.039

	Positive BAT	*Negative BAT*	
With $aTPO^{high}/IgE^{low}$	19	24	43
Without $aTPO^{high}/IgE^{low}$	43	301	344
	62	325	**387**

Diagnostic accuracy	
Sensitivity	30.6%
Specificity	92.6%
PPV	44.2%
NPV	87.5%
Prevalence (pretest probability)	16%
Overall test potential	82.7%
Positive likelihood ratio	4.14
Negative likelihood ratio	0.75
False-positive ratio	7.38%
False-negative ratio	69.35%

FIGURE 1. Diagnostic accuracy analysis. *NPV,* Negative predictive value; *PPV,* positive predictive value.