

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



To the Editor:

We thank Jorge Sanchez and his team for commenting¹ on our recent article² and for performing further analyses on elevated immunoglobulin G (IgG)–anti–thyroid peroxidase (TPO; aTPO) and low total IgE (aTPO^{high}/IgE^{low}) for predicting type IIb autoimmune chronic spontaneous urticaria (aiCSU). The IgG antibodies against IgE and its receptor on mast cells and basophils are thought to drive aiCSU, although IgM, IgA, and IgE autoantibodies that target these antigens have also been detected in some patients with aiCSU. The diagnosis of aiCSU is based on 3 positive tests—the autologous serum skin test (autoreactivity), a basophil test (functionality), and immunoassays (quantitative identification of IgG autoantibodies against FcεRI and/or anti-IgE).³

Importantly, aiCSU comes with high disease activity, high rates of autoimmune comorbidities, poor quality of life, and poor response to treatment with antihistamines and omalizumab.^{3–5} It is, therefore, essential to bring biomarkers and predictors of aiCSU to routine clinical practice. It is also important that these predictors need to be easy to measure and available to all physicians who treat patients with chronic spontaneous urticaria (CSU). In addition to aTPO^{high}/IgE^{low}, other markers that are widely available have been linked to aiCSU including basopenia and eosinopenia.^{2,4,6,7} We fully agree with the notion that the clinical utility of proposed predictors such as the combined use of aTPO and IgE needs to be further evaluated and that the accuracy of this and other biomarkers for CSU including predictors of aiCSU requires confirmation.

Indeed, we ended our recent article² by calling for studies that “better define the strength of the association between aTPO^{high}/IgE^{low} and aiCSU-defining tests, and the predictive values,

sensitivity, and specificity of the former to predict the latter.” Furthermore, other factors that may increase the diagnostic accuracy of aTPO^{high}/IgE^{low}, for example, different cut-off values and/or combination with additional autoimmunity-related markers (eg, basopenia) have to be investigated in further studies (Table 1). For example, the component-resolved screening for autoimmune chronic spontaneous urticaria study⁴ recently investigated a different cut-off value for total IgE (<30 U/mL). Finally, we measured IgE and aTPO levels only at 1 time point, although they can change over time, and this should also be taken into account in upcoming studies.

Here, we double down on our call for further studies. We invite Jorge Sanchez and his team as well as all Urticaria Centers of Reference and Excellence (UCAREs) to help with this effort. The validation of biomarkers is a global task and requires large numbers of samples derived from a diverse population of patients. The UCARE network can help to achieve this goal. To this end, we set up, on the UCARE Website (www.ga2len-ucare.com), a call for all UCAREs to participate in the CU-TIGER project (the characterization of urticaria markers including anti-TPO and IgE in serum). We encourage participation in this UCARE project. Our combined efforts to establish predictors of aiCSU will improve the management of this difficult to treat CSU subtype in clinical practice.

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TABLE 1. Emerging features and markers of autoimmune chronic spontaneous urticaria diagnosed based on basophil testing (BAT and/or BHRA)*

Features/markers	aiCSU	References
Angioedema	Often	2,4
Nocturnal symptoms	Often	4
Symptoms for > 5 d/wk	Often	4
Disease activity (UAS7)	High	2–4
Quality of life (DLQI)	Low	4
Disease control (UCT)	Low	4
Response to omalizumab	Slow and/or poor	5
Total IgE	Low	3,4,7
IgG-anti-TPO	High	3,4
Total IgA	Low	7
Blood basophil counts	Low	3,6
Blood eosinophil counts	Low	6

BAT, basophil activation test; BHRA, basophil histamine release assay; DLQI, dermatology life quality index; UAS7, urticaria activity score for 7 consecutive days; UCT, urticaria control test.

*Basophil testing is the best stand-alone approach for diagnosing autoimmune CSU. It should be performed where available.

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