

Editorial



Anti-TPO IgE Autoantibody in Chronic Urticaria: Is It Clinically Relevant?

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► See the article "Causal Relationship Between Anti-TPO IgE and Chronic Urticaria by *In Vitro* and *In Vivo* Tests" in volume 11 on page 29.

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Chronic spontaneous urticaria (CSU) is a common skin disorder characterized by recurrent itchy wheals, angioedema or both which lasts more than 6 weeks with prevalence of 0.5% to 1%.¹ Although immunologic mechanisms of CSU have not yet been fully understood, it has been suggested that autoimmunity is one of the major cause of activation of mast cells in CSU, where 2 types of autoimmune reactions are involved.^{2,3} Type I autoimmune reaction (autoallergy) is an IgE response reacting to self-antigens that induce mast cells/basophils to release histamine and vasoactive mediators. Type II autoimmunity is explained by the presence of IgG autoantibodies against IgE or high affinity Fc epsilon receptor I (FcεRI), which leads to the degranulation of mast cells/basophils.³ There have been several studies to show a positive association between autoimmune thyroid disease and CSU, and a higher prevalence of serum IgG autoantibody to thyroid peroxidase (TPO) and thyroglobulin (TG) were noted in adult and pediatric patients with CSU.^{3,7} IgG autoantibody to FcεRI was detected in CSU patients which was correlated with autologous serum skin test (ASST) results.⁸ In addition, recent studies demonstrated higher prevalence of IgE autoantibodies to thyroid antigens including TPO in sera of CSU, which could induce activation of basophils, suggesting involvement of IgE-mediated autoimmune mechanism in the pathogenesis of CSU.^{9,10}

In the current issue of *Allergy, Asthma and Immunology Research*, Sánchez *et al.*¹¹ reported a higher prevalence (34%) of serum specific IgE autoantibody against TPO in patients with CSU compared to those with autoimmune thyroid disease (ATD) and healthy controls (NC), when IgG autoantibody was depleted. In addition, peripheral basophils from CSU patients with high anti-TPO IgE autoantibody had higher CD203C expression than those from 2 control groups. They confirmed autoimmune-mediated basophil activation by mixing basophils from CSU and ATD patients with sera with or without anti-TPO IgE autoantibody. Furthermore, as *in vivo* testing, passive transfer of serum from subjects with higher anti-TPO IgE autoantibody to NC subjects (having negative results on skin prick tests with TPO) showed positive skin reactions.¹¹ These results demonstrated that anti-TPO IgE autoantibody plays a crucial role in the autoimmune mechanism of CSU, although it is not enough to be a serum biomarker. Previous reports demonstrated that the prevalence of anti-TPO IgE autoantibody in patients with CSU ranges from 10% to 61%.^{4,12,13} These findings may be attributed to different detection methods applied in individual studies (use of direct ELISA, capture ELISA or modified other commercial available kits) and possible interference by the presence of IgG autoantibody and

other serologic factors in patients with immunologic diseases such as rheumatoid arthritis and *Helicobacter pylori* infection.¹⁴ A recent study suggested IL-24 to be a specific functional autoantigen reacting with IgE autoantibodies in CSU with higher predictable values.¹⁵ High cytokinergic IgE which exhibited polyreactivity to various self-antigens (beta-galactosidase, dsDNA, thyroglobulin, ssDNA and histamine releasing factor) was reported to induce IgE-mediated mast cell degranulation.¹⁶ Further investigations are needed to confirm the role of relevant IgE autoantibodies to self-antigens in the pathogenesis of CSU.

Omalizumab (an IgE antibody which can prevent IgE binding to FcεRI on mast cells/basophils) has been widely applied for treatment of antihistamine-refractory CSU.¹ The clinical efficacy of omalizumab has been found to reduce the urticaria activity score, free IgE level, and expression of FcεRI+ and IgE+ skin cells in the skin tissue of CSU subjects.¹⁷ There have been several studies to predict which patients have favorable responses to omalizumab treatment. Weller *et al.*¹⁸ reported CSU patients with higher serum total IgE level showed favorable responses, while those with lower total IgE levels had unfavorable or delayed responses to anti-IgE antibody treatment. Kaplan *et al.*¹⁹ reported that 4-week omalizumab treatment decreased mean urticaria activity score, declined rescue medication use and improved quality of life in CSU patients with positive autoantibodies. In that study, out of 12 patients, 7 achieved complete remission state, 4 showed symptom improvement and only 1 showed no response to omalizumab treatment. Therefore, anti-IgE antibody is suggested to be an effective treatment option in CSU subjects with high anti-TPO IgE autoantibody, who was refractory to antihistamine treatment.²⁰ These beneficial effects of anti-IgE antibody may be explained by 3 mechanisms: (1) reduced IgE-priming on mast cells, (2) depletion of IgG binding against IgE on mast cells and (3) inhibition of IgE autoantibodies leading to accumulation of IgE-immune complexes, including IgE autoantibodies, to endogenous antigens such as TPO.²¹ Further prospective studies are needed to evaluate the role of autoantibodies in predicting responses to anti-IgE antibody treatment.

In conclusion, circulating IgE autoantibodies to various self-antigens, including TPO, are detectable in a subset of CSU patients, which can contribute to autoimmune mechanisms in the pathogenesis of CSU. Further studies to detect functionally relevant IgE autoantibodies are essential for better control of CSU.

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