Letter to the Editor

Serum transglutaminase 2 activity as a potential biomarker of disease severity and response to omalizumab in chronic spontaneous urticaria

Dear Editor,

Chronic spontaneous urticaria (CSU) is characterized by recurrent hives with or without angioedema lasting for more than 6 weeks; it affects 0.5–1% of the population worldwide. Although CSU is not a life-threatening condition, it has a large impact on quality of life.1,2

The basic treatment for CSU is second-generation H1 antihistamines (H1AH). However, approximately 50% of CSU are not controlled with H1AH, even with increasing doses.3 Cyclosporine and omalizumab - humanized monoclonal anti-IgE antibodies have been suggested as second or third-line therapies for CSU unresponsive to H1AH.1,2 However, there remain a substantial proportion of CSU patients that are not completely responsive to these drugs.1,2

We previously reported that transglutaminase 2 (TG2), an enzyme involved in the posttranslational modification of proteins by deamination and amine incorporation, plays an important role in CSU pathogenesis, showing high expression and release in human mast cells.4 In this study, we investigated the clinical implications of serum TG2 activity as a potential biomarker of disease severity and response to omalizumab treatment.

Subjects were recruited between 2015 and 2017 at the allergy and dermatology outpatient clinic in Hallym University Dongtan Sacred Heart Hospital, and the study was approved by the Institutional Review Board [HDT2014-06-135-003]. We enrolled 111 CSU patients, 31 patients with acute urticaria (AU, male: 48.4%, age: 39.97 ± 14.12), and 45 nonallergic normal controls (NC, male: 28.9%, age: 40.07 ± 17.45). Inducible urticaria was excluded. AU patients were recruited from the emergency room when they had an acute occurrence of urticaria with or without angioedema that was cured within 1 week without recurrence.

CSU patients were divided into four subgroups by disease severity which was decided by treatment levels from the guidelines where several biomarkers have been replicated in different studies.5 Activation of platelets, procoagulation/fibrinolysis participates in the pathogenesis of the CSU is still unclear, nevertheless, D-dimer has been reported to be a biomarker for treatment response to omalizumab and cyclosporine.6,7 Two studies showed D-dimer level was significantly increased in correlation to disease severity (Mild: 87.1 ± 66.3, Moderate: 136.1 ± 64.0, Severe: 159.7 ± 59.0, Very severe: 222.1 ± 68.1 mU/mL, P < 0.001, Supplementary Fig. 1). Serum TG2 activity was significantly increased in correlation to disease severity (Mild: 57.8 ± 24.0, Moderate: 116.6 ± 57.8 mU/mL and NC 70.0 ± 42.4 mU/mL (P < 0.01, Fig. 1A), while no difference was observed between AU and NC. Serum TG2 activity was not significantly different according to sex, ASST, atopy, and angioedema, and it did not correlate with age, blood eosinophil count, or serum total IgE. ROC analysis showed that the differential cutoff value of serum TG2 activity between CSU and AU was 121.1 mU/mL, with sensitivity of 54.1% and specificity of 77.4% (AUC 0.661, 95% CI [0.560–0.762], P = 0.006, Supplementary Fig. 1). Serum TG2 activity was significantly increased in correlation to disease severity and blood eosinophil count or total IgE levels. In the omalizumab-responsive group (n = 9), serum TG2 activity was significantly decreased upon omalizumab treatment at two time points (weeks 2–6 and weeks 16–24, P < 0.01, Fig. 2).

Blood biomarkers of CSU for measuring disease activity, monitoring treatment response, or predicting prognosis are yet to be identified. Although the questionnaires, such as urticaria activity score (UAS), urticaria control test, etc. are validated and useful for the purpose, they are subjective and retrospective.1,2 There have been many attempts to establish useful blood biomarkers in CSU, where several biomarkers have been replicated in different studies. The potential biomarkers for disease activity include D-dimer, C-reactive protein, matrix metalloproteinase-9, mean platelet volume, prothrombin fragment 1 + 2, and interleukin-6.5 Activation of coagulation/fibrinolysis participates in the pathogenesis of the CSU is still unclear, nevertheless, D-dimer has been reported to follow...
the positive or negative clinical response to the treatment via long term follow up period (up to 12 months). Furthermore, total IgE levels have been recently reported to predict the response to omalizumab. A major issue is that these biomarkers, whose levels can be increased due to comorbid conditions, such as chronic infections and autoimmune diseases, are not specific to CSU pathogenesis.

TG2 has been reported to be involved in inflammation of allergic asthma by Th2 differentiation via TG2-mediated IL-33 expression. Hong et al. found that TG2 expressed during mast cell activation enhances IgE production in B cells by up-regulating CD40L expression. We also found that TG2 expression was increased in mast cells in the lesional skin of CSU patients, and that cultured human mast cells derived from peripheral blood or cord blood released TG2 during activation, suggesting that TG2 is involved in the pathogenesis of CSU.

Here, we found that serum TG2 activity was increased with disease severity and decreased after omalizumab treatment. Moreover, serum TG2 activity of CSU was higher than that of AU, showing 121 mU/mL as a differential cutoff value between AU and CSU. Considering the association between TG2 and CSU pathogenesis, serum TG2 activity can be a more specific marker of disease severity and monitoring response to omalizumab treatment in CSU, compared with previously reported biomarkers.

Our study has one limitation that we did not assess the relationship between serum TG2 activity and disease activity, such as UAS. Instead, we assessed ‘disease severity’ which is defined by medication requirement. ‘Disease severity’ in the current study might not reflect the severity of symptoms associated with urticaria.

In conclusion, serum TG2 activity could be a useful biomarker in predicting the medication requirement for disease control. Further study will be needed to confirm this.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.alit.2019.10.009.

Conflict of interest

The authors have no conflict of interest to declare.

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