
Correspondence

EFFECT OF OMALIZUMAB ON PATIENTS WITH CHRONIC URTICARIA: ISSUES WITH THE DETERMINATION OF AUTOIMMUNE URTICARIA

To the Editor:

The article by Spector and Tan¹ describes 3 cases of chronic urticaria (CU) showing remarkable response to omalizumab. Although I agree with the authors that this improvement with omalizumab is intriguing, I do not agree that there is good evidence to say that patients 1 and 3 have autoimmune urticaria related to anti-IgE receptor autoantibodies.

Although the National Jewish Reference Laboratory gives a reference range of 0% to 5% for their assay, this reference range really only applies to *nonurticaria* normal controls. In the published data,² cited also by Spector and Tan, although the *nonurticaria* normal controls all had CD203c expression less than 5%, some nonautoimmune (negative autologous serum skin test [ASST] result) CU patients had CD203c expression higher than 5%, in fact as high as 20% to 30%.² Even excluding these patients, it was still found that the sera from nonautoimmune CU patients could still induce CD203c expression, more so than in controls. In their conclusion, the National Jewish Reference Laboratory authors state, "Twenty percent of patients' sera with negative ASSTs induced >5% basophil activation compared with buffer control. . . . It is an interesting observation that the sera from ASST- patients induced significantly higher CD203c expression than normal controls, although still significantly lower than ASST+ patients. . . . This finding suggests that there are other undefined serum factors present in CU sera that can upregulate CD203c."²

So, based on this statement, it is possible for CU patients to have a positive CD203c assay, but yet the mechanism of urticaria may be independent from anti-IgE receptor autoantibodies. Other data have suggested that there may also be similar false-positive results with basophil histamine release assays, where patients may have a positive assay but yet the mechanism of urticaria is completely unrelated.³ Spector and Tan's patient 1 had a CD203c assay level of 9.1%,¹ very close to the reference range of 0% to 5%, so this may not be a truly abnormal result. Furthermore, patient 1 had a negative result on the in vitro histamine release test. As the authors suggest, performing an ASST on patient 1 may have been of additional help in determining autoimmunity status. They report that the CD203c result "normalized" to 1.6% after 6 months. Although intriguing, given the issues discussed herein and the likely variability from day to day with the CD203c assay, I do not find this to be convincing. Patient 3 had a CD203c result of 6.1%, barely above the reference range of 0% to 5%. They

report that the in vitro histamine release test was positive at 18%, but again, since this is only slightly higher than the reference range of 0% to 16.5% release, I find it unconvincing since it could represent a false-positive result.

I agree with Spector and Tan's discussion of the hypothetical ways that omalizumab may help in treating CU. However, there is one possibility that they did not mention. Data now indicate that structural and functional abnormalities in basophils may play a pathophysiological role in CU.^{3,4} Vonakis et al⁵ have reported 2 subtypes of CU based on the histamine-release response of the patients' basophils, with no correlation to anti-IgE receptor antibodies (which were found to occur in both groups). It is possible that the down-regulation of the IgE receptor caused by omalizumab may cause functional and activational changes in the abnormal basophils and/or mast cells in these patients, in essence "quietening them down."

In conclusion, we must be careful in interpreting the results of the National Jewish Reference Laboratory CD203c and similar autoimmune urticaria assays. A result outside the reported reference range does not necessarily mean that the mechanism of urticaria is autoimmune because of anti-IgE receptor autoantibodies.

JAVED SHEIKH, MD
Division of Allergy & Inflammation
Beth Israel Deaconess Medical Center
Harvard Medical School
Boston, Massachusetts

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The above correspondence was referred to the original authors who provided the following response:
We thank Dr Sheikh for his thoughtful comments on our article.

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The National Jewish Reference Laboratory responds: “. . . we have collected data from over two years of running the assay for patients with chronic urticaria, [and] we are preparing a manuscript. We agree that the CD203c assay is a biological assay inherently subject to variability, much as is the histamine release assay. We agree that specificity and sensitivity need to be quantified, and we are in the process of working with our biostatisticians to set thresholds.”

In addition to the possible mechanism that Dr Sheikh

mentioned, down-regulation of the IgE receptor may also affect the survival of mast cells.¹

SHELDON SPECTOR, MD
RICARDO TAN, MD
California Allergy & Asthma Medical Group
Los Angeles, California

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