## Selective IgE Deficiency Predicts Poor or No Response of Chronic Spontaneous Urticaria to Omalizumab

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Selective immunoglobulin E deficiency (SIgED) has been associated with autoimmunity, airway infections, asthma, enteropathy, chronic spontaneous urticaria (CSU), and malignancy [1-3].

CSU is a mast cell–driven disease characterized by itchy hives that is frequently associated with angioedema [4]. While the cause of CSU remains open to debate, some cases have been linked to autoimmune mechanisms mediated by IgE autoantibodies (type I) or by IgG antibodies (type II) [4].

Omalizumab (a recombinant, humanized anti-IgE antibody) binds IgE and reduces levels of both free IgE and FcεR1 expression on mast cells and basophils [4].

Treatment guidelines recommend a 4-step approach for the management of CSU. Omalizumab is included in the third line as add-on therapy to second-generation H1-antihistamines (H1-AHs). In patients whose disease remains inadequately controlled with omalizumab, treatment with immunosuppressive drugs, such as cyclosporine, is recommended as a fourth-line approach. Response to treatment is generally measured using the Urticaria Activity Score (UAS7) [5].

The licensed dose of omalizumab in Europe is 300 mg administered every 4 weeks. However, augmenting the dose or shortening dosing intervals may provide better symptom control in patients with a limited response to the 300-mg dose [6].

Low IgE levels, low blood basophil counts, and low blood eosinophil counts prior to initiation of omalizumab are associated with reduced clinical efficacy [7]. We tested the hypothesis that patients with SIgED comprise the group with the poorest response to omalizumab.

We retrospectively evaluated 6 patients with CSU associated with SIgED (IgE ≤2 kU/L) and treated with omalizumab from a recently reported cohort of patients [3]. The study was approved by the local ethics committee.

Demographic data, disease features, comorbidities, laboratory results, omalizumab dosage, and treatment outcomes were collected. All patients were female, with ages ranging from 46 to 66 years. In 4 patients, CSU was associated with angioedema. Three patients had associated immune diseases. IgG anti-thyroid peroxidase (aTPO) was elevated in 4 of the 5 patients tested; D-dimer was elevated in 3. Low blood basophil counts were observed in all but 1 patient, while significantly low eosinophil counts were present in 2 patients (Table).

None of the patients achieved adequate control with the maximum oral H1-AH dose, and they all required frequent oral corticosteroid treatment to control CSU flares. Patients were initially treated with a 300-mg monthly dose of omalizumab. When a partial or null response to omalizumab was observed based on the UAS7 score, either the omalizumab dose was increased or immunosuppressive drugs were administered at the recommended doses. These were then tailored individually according to disease response and drug tolerability. A brief description of the patients follows.

Patient 1 received omalizumab 300 mg monthly but continued to have significant urticaria and angioedema; thus, the dose was increased to 450 mg monthly and later to 600 mg monthly without achieving control. During a 7-year follow-up, the patient was treated with cyclosporine (100-200 mg/d) followed by methotrexate, although urticaria was only partially controlled. Finally, treatment with dapsone (doses between 75 and 100 mg daily) led to total control of urticaria in the last year of follow-up.

Patient 2 initiated omalizumab 300 mg monthly without response. Treatment was increased to 450 mg monthly, with only partial control being achieved. Cyclosporine was added at an initial 200 mg/d, which had to be reduced to 100 mg/d owing to adverse effects. The combination enabled better control, although symptoms with greater or less intensity persisted with fluctuations.

Patient 3 had had a history of urticaria since the age of 15. This was initially treated with colchicine and dapsone (2004-2007), neither of which was successful. Subsequent treatment with cyclosporine (100-150 mg day) achieved good control of CSU. In 2007, she was diagnosed with autoimmune hepatitis and began treatment with azathioprine and oral prednisone at doses of 7.5 to 15 mg. Her CSU remains partially controlled. The patient was treated with omalizumab (300 mg monthly) for 1 year, although this was unsuccessful. Treatment was discontinued. Azathioprine was replaced by mycophenolate mofetil at doses ranging from 1.5 to 2 mg/d. The patient's hepatitis and CSU have remained under control without the need for oral prednisone during the last 5 years of follow-up.

Patient 4 initiated treatment with omalizumab 300 mg monthly and achieved a partial response. Omalizumab was increased to 450 mg monthly with good control for 8 months, although control of the disease was again lost and the dose was further increased to 600 mg monthly, achieving total control for 26 months. The patient decided to discontinue treatment and has remained without further urticaria/angioedema symptoms during a 17-month follow-up.

**Table.** Summary of 6 Patients With Chronic Spontaneous Urticaria and Selective IgE Deficiency

| Patient no. | Age/Sex | CSU/CSU+A | aTPO (<35) | D-dimer (<500) | Autoimmune diseases | Autoimmune therapy |
|---|---|---|---|---|---|---|
| 1 | 53/F | CSU | 45 | 600 | None | Cyclosporine Methotrexate Dapsone |
| 2 | 66/F | CSU+A | 83 | 590 | Neutropenia Hypothyroidism | Cyclosporine |
| 3 | 46/F | CSU+A | ND | ND | Autoimmune hepatitis | Cyclosporine Mycophenolate |
| 4 | 60/F | CSU+A | 61 | ND | Vitiligo Hypothyroidism | Cyclosporine |
| 5 | 53/F | CSU | 83 | 1200 | None | Cyclosporine |
| 6 | 64/F | CSU+A | 28 | ND | None | Cyclosporine Methotrexate |

Abbreviations: A, angioedema; aTPO, IgG antithyroid peroxidase; CSU, chronic spontaneous urticaria; F, female; ND, not determined.

Patient 5 was initially treated with omalizumab 300 mg monthly for 6 months without response. She was then treated with cyclosporine (100-200 mg daily), leading to total control of urticaria. The cyclosporine dose was progressively decreased and discontinued (7 months). The patient remained asymptomatic for 22 months until urticaria relapsed. Omalizumab 300 mg monthly was initiated for 3 months, with no effect. Cyclosporine was then prescribed (200 mg), leading to total control. The dose was tapered to 50-75 mg/d, and urticaria has remained well controlled for 17 months.

Patient 6 received various treatments over 19 months: omalizumab (300 mg monthly and 450 mg every 2 weeks), followed by cyclosporine (doses between 200 mg and 50 mg daily) and methotrexate (10 mg/wk). The patient continued to experience repeated outbreaks of urticaria and angioedema, which were treated with systemic corticosteroids. Urticaria and angioedema disappeared suddenly when the emotional stress she had been experiencing from the outset of the CSU ceased.

Four patients had high aTPO level, 3 had high D-dimer levels, 5 had low blood basophil counts, and 3 had autoimmune diseases, generally linked to type II CSU [8]. One patient appeared to have stress-induced CSU [9].

The limitations of our study include the low number of patients included and the fact that treatment was not always strictly applied according to guidelines. In 1 patient, the drug was chosen to simultaneously treat CSU and autoimmune hepatitis.

In summary, our study highlights the potential relevance of diagnosing SIgED, which is often missed because ultralow IgE levels are generally considered "normal" when predicting lack of response of CSU to omalizumab.

## References

1. Smith JK, Krishnaswamy GH, Dykes R, Reynolds S, Berk SL. Clinical manifestations of IgE hypogammaglobulinemia. Ann Allergy Asthma Immunol. 1997;78:313-8. doi: 10.1016/S1081-1206(10)63188.

2. Magen E, Schlesinger M, David M, Ben-Zion I, Vardy D. Selective IgE deficiency, immune dysregulation, and autoimmunity. Allergy Asthma Proc. 2014;35:e27-e33. doi: 10.2500/aap.2014.35.3734.

3. Picado C, de Ortiz de Landazuri I, Vlagea A, Bobolea I, Arismendi E, Amaro R, et al. Spectrum of Disease Manifestations in Patients with Selective Immunoglobulin E Deficiency. J Clin Med. 2021;10:4160. doi: 10.3390/jcm10184160.

4. Maurer M, Khan DA, Elieh Ali Komi D, Kaplan AP. Biologics for the Use in Chronic Spontaneous Urticaria: When and Which. J Allergy Clin Immunol Pract. 2021;9:1067-78. doi: 10.1016/j.jaip.2020.11.043.

5. Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B, et al. The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy. 2018;73:1393-414. doi: 10.1111/all.13397.

6. Maoz-Segal R, Levy T, Haj-Yahia S, Offengenden I, Iancovich-Kidon M, Agmon-Levin N. Combination therapy with omalizumab and an immune-suppressive agent for resistant chronic spontaneous urticaria - A real-life experience. World Allergy Organ J. 2020;13:100448. doi: 10.1016/j.waojou.2020.100448.

7. Fok JS, Kolkhir P, Church MK, Maurer M. Predictors of treatment response in chronic spontaneous urticaria. Allergy. 2021;76:2965-81. doi: 10.1111/all.14757.

8. 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. doi: 10.1016/j.jaip.2021.07.043.

9. Schut C, Magerl M, Hawro T, Kupfer J, Rose M, Gieler U, et al. Disease activity and stress are linked in a subpopulation of chronic spontaneous urticaria patients. Allergy. 2020;75:224-6. doi: 10.1111/all.14015.

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