Selective IgE deficiency predicts poor or no response of chronic spontaneous urticaria to omalizumab

Picado C[1,2], Mascaró JM Jr[1,2,3], Vlagea A[4], Pascal M[1,2,4], Muñoz-Cano R[1,2,5], Bartra J[1,2,5]

[1]Hospital Clinic. University of Barcelona, Barcelona, Spain

[2]Institut d'Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS), Barcelona, Spain

[3]Department of Dermatology, Hospital Clinic, Barcelona, Spain

[4]Department of Immunology, CDB, Hospital Clinic, Barcelona, Spain

[5]Department of Allergy, Hospital Clinic, Barcelona, Spain

Corresponding author:

Dr. César Picado

Hospital Clinic.

Villarroel 170. 08036 Barcelona. Spain.

E-mail: cpicado@ub.edu

Accepted Article

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.18176/jiaci.0796

© 2022 Esmon Publicidad

Key words: Angioedema. Immunoglobulin E. Immunodeficiency. Omalizumab. Urticaria.

Palabras clave: Angioedema. Inmunoglobulina E. Inmunodeficiencia. Omalizumab. Urticaria.

Selective immunoglobulin E deficiency (SIgED) has been reported 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 frequently associated with angioedema [4]. Although the cause is still being debated, some CSU cases have been linked to autoimmune mechanisms either 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 four-step approach for CSU management. Omalizumab is included in the third line as add-on therapy to second-generation H1-antihistamines (H1-AHs). In patients who remain inadequately controlled with omalizumab, treatment with immunosuppressive drugs, such as cyclosporine, is recommended as a fourth-line drug. Response to treatment is usually measured with the Urticaria Activity Score (UAS7)[5].

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

It has been shown that low IgE levels, basopenia and eosinopenia prior to initiation of omalizumab therapy are associated with a reduced clinical efficacy [7]. We tested the hypothesis that patients with SIgED would represent the group of patients with the poorest response to omalizumab.

We retrospectively evaluated six patients with CSU associated with SIgED (IgE ≤2 kU /L) and treated with omalizumab, from a cohort of patients reported recently [3]. The study was approved by the 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 four patients, CSU was associated with angioedema. Three patients had associated immune diseases. IgG anti-thyroid peroxidase (aTPO) was found elevated in four among five patients tested, while D-Dimer was assessed and found elevated in three. All but one patient were basopenic, while significant eosinopenia was present in two patients (Table 1).

None of the patients achieved adequate control with maximum oral H1-AH dose, and they all also required frequent oral corticosteroid treatment to control flares of CSU. 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

Accepted Article

 © 2022 Esmon Publicidad
doi: 10.18176/jiaci.0796

the omalizumab dose was increased or immunosuppressive drugs were administered at the usual recommended doses, which were 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 seven-year follow-up, the patient was treated with cyclosporine (100-200 mg/day) followed by methotrexate, but only partial control of the urticaria was achieved. Finally, the patient was treated with dapsone (doses between 75 and 100 mg daily) and total control of urticaria was achieved in the last year of follow-up.

Patient 2 initiated omalizumab 300 mg monthly without response and treatment was increased to 450 mg monthly, only achieving partial control. Cyclosporine was added at an initial 200 mg/day dose that had to be reduced to 100 mg daily due to side effects. The combination allowed better control, although the symptoms with greater or less intensity persisted with fluctuations.

Patient 3 has a history of urticaria since the age of 15, initially treated with colchicine and dapsone (2004-2007) without result. Subsequent treatment with cyclosporin (100-150 mg day) achieved good control of the CSU. In 2007 she was diagnosed with autoimmune hepatitis and began treatment with azathioprine and oral prednisone at doses of between 7.5 and 15 mg. The CSU remains partially controlled. The patient was treated with omalizumab (300 mg monthly) for one year with no result and the treatment was discontinued. Azathioprine was substituted by mycophenolate mofetil at doses ranging from 1.5-2 mg/day. Hepatitis and CSU remain under control without the need for oral prednisone during the last five years of follow-up.

Patient 4 initiated treatment with omalizumab 300 mg monthly showing a partial response. Omalizumab was increased to 450 mg monthly with good control for eight months, but again control was 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.

Patient 5, was initially treated with omalizumab 300 mg monthly for six months without response. She was treated with cyclosporine (100-200 mg daily) and total control of urticaria was achieved. The cyclosporin dose was progressively decreased and discontinued (seven months). The patient remained asymptomatic for 22 months until urticaria relapsed. Omalizumab 300 mg monthly was initiated for three months without any effect, and cyclosporine was indicated (200mg) and total control achieved. The dose was tapered to 50-75 mg/day 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 two weeks), subsequently cyclosporine (doses between 200 mg and 50 mg daily) and methotrexate (10 mg/week). The patient continued with repeated outbreaks of urticaria and angioedema treated with systemic corticosteroids. Urticaria and angioedema suddenly disappeared when the emotional stress she was suffering from the outset of the CSU ceased.

Four patients had high aTPO, three high D-Dimer, five basopenia and three autoimmune diseases, usually linked to Type II CSU [8], and one appeared to have stress-induced CSU [9].

Accepted Article

 © 2022 Esmon Publicidad
doi: 10.18176/jiaci.0796

Limitations of our study include the low number of patients recruited retrospectively and that treatment was not always strictly applied according to guidelines. In one patient, treatment 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"- in predicting lack of response of CSU to omalizumab.

Funding

This study has not received any financial support.

Conflicts of interest

C.P. reports having served as a consultant to Novartis and Roche, and having been paid lecture fees by Novartis, GSK, and Merck. J-M. MJr. has been paid lectures fees by Janssen, LEO Pharma Spain, and Sanofi-Aventis. M.P. has been paid lecture fees by ThermoFisher Scientific. J.B reports having served as a consultant to Novatis, and having paid lecture fees by Novartis, Leti, ALK and ThermoFisher Scientific. A.V., R. MC., and J.B., declare no conflicts of interest.

Accepted Article

© 2022 Esmon Publicidad
doi: 10.18176/jiaci.0796

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. 2021:15;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;76:2965-2981. 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;9:4138-4146.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.

Accepted Article

© 2022 Esmon Publicidad
doi: 10.18176/jiaci.0796

Table. Summary of six patients with CSU and SIgEd.

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	1.200	None	**Cyclosporine**
6	64F	CSU+A	28	ND	None	**Cyclosporine Methotrexate**

A=angioedema; F=female; ND=not determined; aTPO=IgG anti-thyroid peroxidase (aTPO) ; CSU=Chronic Spontaneous Urticaria

Accepted Article

© 2022 Esmon Publicidad