

Immunological Effects of Omalizumab in Chronic Urticaria: A Case Report

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■ Abstract

We describe a case of chronic idiopathic urticaria in which symptoms improved dramatically after treatment with omalizumab. This drug, which is approved for the treatment of asthma, has been studied in other allergic conditions and a number of reports have described its efficacy as an immunomodulator in chronic and physical urticaria.

Immunopathologic mechanisms are poorly understood. In chronic autoimmune urticaria, it has been postulated that this monoclonal antibody against immunoglobulin (Ig) E might reduce FcεRI expression on the surface of basophils, thus preventing IgG antibody-mediated crosslinking and the release of mast cell mediators.

We analyzed activation and homing molecules of B cells and type 1 and type 2 cytokine production by T cells and document a new immunomodulator mechanism characterized by a reduction in B-cell activation and homing and in tumor necrosis factor-α and interleukin 4 production and an increase in interferon-γ synthesis.

Key words: Chronic urticaria. Anti IgE. Omalizumab. B cell.

■ Resumen

Se describe un caso de urticaria idiopática crónica cuyos síntomas mejoraron considerablemente después del tratamiento con omalizumab. Este fármaco, que está aprobado para el tratamiento del asma, se ha estudiado en otras enfermedades alérgicas y varios informes han descrito su eficacia como inmunomodulador en la urticaria crónica y física.

Los mecanismos inmunopatológicos todavía no se conocen bien. En la urticaria autoinmune crónica se ha sugerido que este anticuerpo monoclonal contra la inmunoglobulina (Ig) E podría reducir la expresión de FcεRI en la superficie de los basófilos, y evitar así el entrecruzamiento mediado por anticuerpos IgG y la liberación de mediadores de los mastocitos.

Se analizó la activación y moléculas "homing" de linfocitos B y la producción de citocinas de tipo 1 y tipo 2 por parte de linfocitos T y se documentó un nuevo mecanismo inmunomodulador, caracterizado por una reducción de la activación y "homing" de los linfocitos B, una disminución del factor de necrosis tumoral-α y de la producción de interleucina 4 y un aumento de la síntesis de interferón-γ.

Palabras clave: Urticaria crónica. Anticuerpo anti-IgE. Omalizumab. Linfocito B

Chronic idiopathic urticaria (CIU) affects 1% to 3% of people in western countries and has a considerable impact on quality of life, as noted by Baiardini [1]. The evidence-based approach to treatment with antihistamines [2] is not always helpful in solving itching and hives. A discussion of the limitations of antihistamine therapy and treatment alternatives is given in [3]. Many studies show that the etiology of CIU is an immunological disorder [4] but other mechanisms have been suggested [5]. Of the therapies which have been used in antihistamine-resistant CIU, corticosteroids and immunosuppressive drugs have shown to be useful; these drugs are nevertheless associated with adverse effects that limit their use over long periods of time.

Omalizumab is a recombinant, humanized, monoclonal antibody directed toward immunoglobulin (Ig) E that is approved for the treatment of severe uncontrolled allergic asthma. The drug has also been used in the treatment of allergic rhinitis, atopic dermatitis, mastocytosis, and food allergy, as well as an adjuvant in allergen immunotherapy and urticaria. Omalizumab has also been used in a patient treated for moderate asthma, with complete remission of cold-induced urticaria, as noted by Boyce [6].

Additionally, a number of reports indicate a possible efficacy of this immunomodulator in physical and chronic urticaria and angioedema [7-11].

Case Description

We describe the case of a 57-year-old white woman with chronic urticaria/angioedema syndrome since 2001. She had been previously studied for allergy diseases with negative results (prick test and CAP system assay) and treated with corticosteroids, antihistamines, and antileukotrienes.

In October 2006, she underwent a complete laboratory examination, a chest X-ray, an abdominal ultrasound, dental orthopantomography, a urea breath test, and psychological and physical evaluation. Autologous skin tests (plasma and serum, also with the addition of heparin) were performed, with negative results. IgE was 700.

The patient was treated with cyclosporine (3 mg/kg/day), with only partial relief, and subsequently with colchicine (1 mg/day), hydroxychloroquine (3 mg/kg/day), azathioprine (2 mg/kg/day) and intravenous immunoglobulins (0.4 g/kg/month). No significant changes in signs or symptoms were observed and during these therapies the patients had to take periodic cycles of corticosteroids and daily antihistamines.

Because of her elevated IgE levels, 2 months later the patient was started on omalizumab therapy (300 mg subcutaneously every 2 weeks), with a dramatic improvement in symptoms and complete resolution of the urticaria a few days after the first injection. She was treated with omalizumab for 6 months. After 1 month of treatment interruption, the urticaria reappeared. Omalizumab therapy was restarted, and led to a new rapid improvement of symptoms after the first injection.

Discussion

Kaplan et al [8] suggested that omalizumab can reduce the expression of FcεRI on the surface of basophils and prevent both IgG antibody-mediated crosslinking in chronic autoimmune urticaria and the release of mast cell mediators. Noga et al [12] added to this body of knowledge by showing that the anti-inflammatory activity of omalizumab depended on the induction of eosinophil apoptosis and the downregulation of the inflammatory cytokines interleukin (IL) 2 and IL-13.

We analyzed activation and homing molecules of B cells and type 1 and type 2 cytokine production by T cells before omalizumab therapy (baseline), at the end of the first treatment cycle (month 6), after 1 month of treatment interruption (month 7), and after 1 month of the second cycle of omalizumab therapy (month 8).

At baseline, the percentage of activated B cells (CD19/CD80, CD19/CD86) and migration markers (CCR9, CCR10) were higher in our patient than in a group of healthy controls. At the end of the first omalizumab treatment cycle, we observed a significant decline in both activation and homing markers to normal levels. At treatment interruption (month 7), the majority of these parameters increased again to levels higher than at the end of the first treatment (month 6). After an additional month of omalizumab therapy, the immunological markers diminished except for CD19/CD86 (Table). A similar scenario was observed when we analyzed baseline and stimulated (seb plus anti-CD28) tumor necrosis factor-α and IL-4 production (data not shown). Interestingly, interferon (IFN)-γ synthesis showed the opposite behavior (Table).

Our data confirm the clinical efficacy of omalizumab in the treatment of CIU. Moreover, they suggest a new immunomodulator mechanism of anti-IgE therapy characterized by a reduction in B-cell activation and homing and TNF-α and IL-4 production and an increase in IFN-γ synthesis.

Whether or not the drug elicits a rapid clinical response is an important factor to take into account when decisions regarding treatment continuation need to be taken. Finally, it should be borne in mind that, as occurs in patients with asthma, symptoms may return when the drug is stopped.

References

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Table. Activation and Homing Markers and Stimulated Cytokine Production in an Omalizumab-Treated Patient

Time Points	CD19/CD80 ^a	CD19/VD86 ^a	CD19/CCR9 ^a	CD19/CCR10 ^a	CD4/IL-4 ^a	CD4/TNF-α ^a	CD4/IFN-γ ^a
Baseline	16.5	87.8	3.6	4.7	0.7	4.5	0.6
Month 6	8.4	4.8	1.1	3.4	0.2	1.2	0.3
Month 7	11.4	5.9	11.5	4.9	2.1	8.1	1.4
Month 8	10.9	6.1	2.9	2.1	0.6	3.0	4.9
Levels in healthy controls ^b	4.85 (0.58)	5.15 (0.21)	2.5 (0.08)	2.7 (0.06)	0.47 (0.02)	3.0 (0.11)	1.05 (0.03)

Abbreviations: IFN, interferon; IL, interleukin; TNF, tumor necrosis factor.

^aPercentage of positive cells.

^bMean (SEM) percentage of positive cells.

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