

Letter to the Editor

Omalizumab is effective in nonautoimmune urticaria

To the Editor:

We performed an open prospective observational study to assess whether omalizumab is effective treatment of patients with nonautoimmune chronic urticaria who are unresponsive to antihistamines, and in some instances, unresponsive to low-dose corticosteroid and/or cyclosporine. We included the first 9 consecutive patients with severe nonautoimmune chronic urticaria who fulfilled the aforementioned criteria. The patients were designated “nonautoimmune” by measuring histamine release (1.22; interquartile range [IR] 0-9.9), and CD63 expression (0.62; IR 0-4.4) on incubation of patients' sera with donor basophils, and all subjects were negative.

To assess basophil responsiveness to anti-IgE for the histamine release, we incubated isolated leukocytes with goat antihuman IgE (Tago; Caltag, Burlingame, Calif), and for the CD63 expression, with monoclonal anti-FcεRI (1 μg/mL; BÜHLMANN, Schönenbuch, Switzerland) and assayed histamine release and CD63 expression as previously described.¹⁻³ Basophil number was counted by flow cytometry using dual staining with rat anti-IgE-fluorescein isothiocyanate (Caltag, Buckingham, United Kingdom) and CD63-phycoerythrin (BD Biosciences, San Diego, Calif). We designated basopenia to be present with a count of less than 50 basophils analyzed in 3 minutes by FACS Diva Software in a FACS Canto Cytometre (BD Biosciences). We measured antithyroid antibodies in all patients except patient 7, and all were negative for antithyroglobulin and antimicrosomal antibodies. We determined antinuclear antibodies in 3 of these patients; 2 were negative, and 1 (patient 3) was positive.

We obtained permission for the compassionate use of omalizumab from the National Ministry of Health as well as informed consent from each patient. We administered 300 mg omalizumab subcutaneously to all patients, regardless of the total IgE level.

We administered monthly doses to 5 patients, a dose every 3 months to 3 patients, and a bimonthly dose to 1 patient. The patient demographics are summarized in Table I. We used the “urticaria activity score”^{4,5} to evaluate urticaria severity and symptom improvement (Table II). There were no dropouts.

For statistical analysis, we pooled the medications by therapeutic dose intervals—that is, the sum of the number of tablets of antihistamines, montelukast, and cyclosporine taken and total milligrams taken for corticosteroids. Patients were allowed to take medication as needed, and the number of pills or milligrams of corticosteroids per day was recorded. These data do not correspond to a normal distribution; thus, values are expressed as medians and interquartile ranks. We used the Mann-Whitney *U* test to compare nonnormally distributed quantitative values and the Fisher exact test or the χ^2 test for qualitative variable comparisons. Software SPSS (IBM Corporation, New York, NY) 13.0 was used.

Patients 2 and 4 (Table I) achieved a complete remission after 1 and 2 doses of omalizumab, respectively; patient 2 remained asymptomatic for 2 years and patient 4 for 18 months. Two patients were free of symptoms between doses, meaning that we continued omalizumab on a regular basis and did not wait for hives to reappear. Five patients typically had a few hives or mild pruritus just before the next dose.

We found significant Urticaria Activity Score (UAS) among pretreatment and second, third, and fourth doses. Both variables—that is, pruritus and number of urticarial lesions—were also significantly reduced. We found significant improvement in the requirements for *ad libitum* medication (Fig 1). Only 3 patients required the use of any antihistamine; 1 patient took 10 mg cetirizine per day, another 10 mg levocetirizine per day, and the third patient 30 mg desloratadine daily. Patient 8 received a monthly dose, was able to reduce corticosteroids, and remained asymptomatic from the day after omalizumab was given. However, several days before the dose, hives and pruritus reappeared.

Five of 9 patients had basopenia. However, patients' basophil counts did not change significantly during treatment (pretreatment: 30, IR 18-99; second dose: 65, IR 24.5-157; third dose: 54.5, IR 15.8-285.7). Patient 2, who had been asymptomatic for 2 years subsequent to the last dose, had an increase in basophil count to normal (pretreatment, 30; second dose, 0; third dose, 0; after 5 months of remission, 179; after 7 months, 92; after 12 months, 77; after 18 months, 204 basophils), whereas the second patient, patient 4, had a sustained remission but remained basopenic.

We observed low histamine release on incubation of patients' basophils with anti-IgE (pretreatment: 0, IR 0-20.4; second

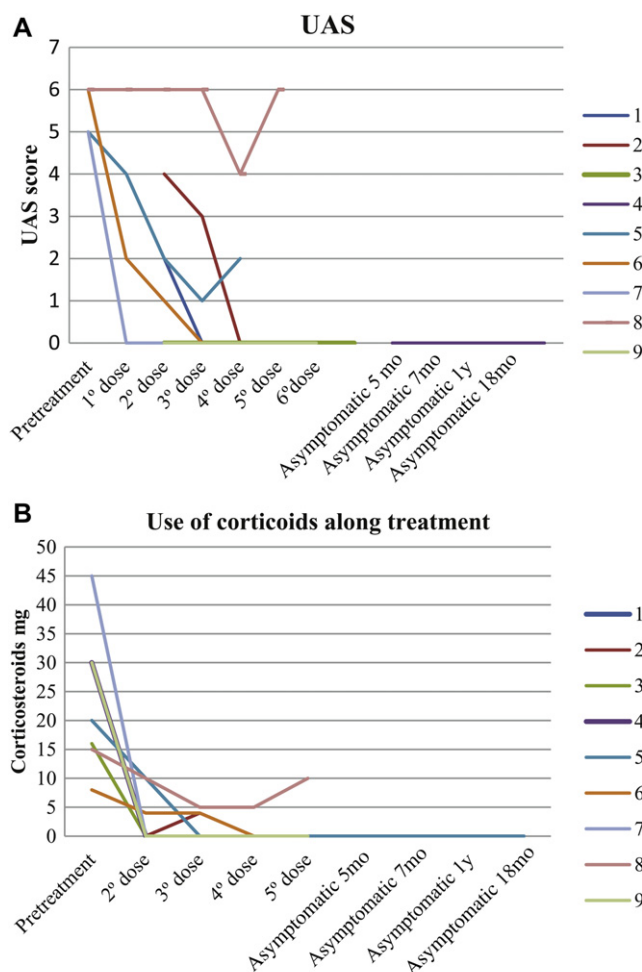
TABLE I. Demographics of the patients included in the study

Patient no.	Age (y)	Sex	Chronic urticaria duration	Pretreatment medication (mg)	Angioedema	Biopsy	Total IgE (IU/L)	Allergies (rhinitis)
1	46	M	7 y	Cyclosporine 300; ranitidine 150; omeprazole 20	Yes	Yes	114	No
2	52	M	5 y	Levocetirizine 10; prednisone 30	No	No	10.9	No
3	45	F	6 y	Deflazacort 30; doxepin 25; cetirizine 10; levocetirizine 10	No	No	95.4	No
4	58	F	11 y	Hydroxyzine 125	Yes	Yes	12.8	No
5	19	F	6 y	Levocetirizine 10; prednisone 20; cyclosporine 300 (withdraw poor tolerance)	Yes	Yes	1940	Grass, mouse dust mites
6	48	F	7 y	Prednisone 20; levocetirizine 10	Yes	Yes	80	No
7	33	F	10 y	Methylprednisolone 30; levocetirizine 10	No	Yes	173	House dust mites
8	37	F	6 mo	Prednisone 30; levocetirizine 10	Yes	No	32.4	Grass
9	56	F	7 y	Prednisone 15; doxepin 150; cetirizine 15; fexofenadine 180; montelukast 10	Yes	Yes	2.6	No

F, Female; M, male.

TABLE II. Symptom score and use of medication

Dose	Urticaria activity score			Use of medication		
	Median	IR	P	Median	IR	P
Pretreatment	6	5-6		32	22.5-42	
2nd	1	0-3	.023	2.5	0-8	.012
3rd	0	0-3	.025	0	0-3	.018
4th	0	0-2	.039	0.5	0-5	.028

**FIG 1.** **A**, Urticaria activity score in 9 nonautoimmune patients with chronic urticaria treated with omalizumab. The score, from 0 to 6, quantifies hive number, pruritus, and interference with daily activities and sleep. **B**, Dose of corticosteroids employed along with treatment with omalizumab.

dose: 2.4, IR 1-35.2; third dose: 14.9, IR 6.9-39.9; fourth dose: 11, IR 0.17-22.5) and CD63 expression (pretreatment: 7.1, IR 0-53.7; second dose: 0.7, IR 0-5.6; third dose: 19.7, IR 0-39; fourth dose: 3.1, IR 0-7.8). However, this feature did not change with treatment. Regarding patients who remained asymptomatic after treatment, the 1 patient whose basopenia reversed recovered the ability to release histamine and express CD63 on incubation with anti-IgE and anti-FcεRI receptor, respectively. In contrast, the patient who remained asymptomatic for 18 months and

remained basopenic did not increase histamine release or CD63 expression on stimulation with anti-IgE. There were no changes in response to autologous serum as assessed by expression of CD63 or histamine release.

We report herein a dramatic response to omalizumab in severe patients with chronic urticaria who were unresponsive to high doses of antihistamines, corticosteroids, and in some cases, cyclosporine in the absence of antibody to the IgE receptor or to IgE as assessed by basophil histamine release. In the current study, we did not observe any immunologic changes associated with this effect. One possible explanation is that the efficacy of omalizumab is subject to perturbation of the cells such as mast cells, eosinophils,⁶ or basophils that depend on FcεRI or IgE even in the absence of autoantibody. Another alternative is that omalizumab might prevent FcεRI dependent-secretion of cytokines and chemokines⁷ by a stimulus that is as yet unknown.

Regardless, all patients reported rapid relief of hives and pruritus, sometimes within 48 hours after the omalizumab injection. In previous studies that measured FcεRI kinetics after omalizumab treatment,^{6,8,9} significant downregulation of receptor numbers took at least several days. It seems unlikely that omalizumab could produce a decrease in IgE receptor density in an even shorter interval. Thus rapid reduction of plasma IgE levels might nonspecifically downregulate responsiveness of cutaneous mast cells and/or basophils by mechanisms not yet determined that are independent of surface IgE receptor density.

In conclusion, omalizumab can affect the course of chronic urticaria, dramatically in some instances, even in the absence of anti-IgE receptor antibody. This outcome, apart from offering a promising treatment for a highly disabling disease, offers new approaches to the study of chronic urticaria pathophysiology given the multiplicity of effects of omalizumab therapy. Large clinical trials will be needed to establish its indication as a therapy for chronic urticaria, particularly when it is resistant to antihistamines, and to determine the best protocol for drug administration.

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