Treatment of chronic autoimmune urticaria with omalizumab

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Background: Approximately 45% of patients with chronic urticaria have an IgG autoantibody directed to the α-subunit of the high-affinity IgE receptor (chronic autoimmune urticaria, CAU) leading to cutaneous mast cell and basophil activation. Treatment of allergic asthma with omalizumab produces rapid reduction in free IgE levels and subsequent decrease in FcεRI expression on mast cells and basophils. If this occurs in CAU, cross-linking of IgE receptors by autoantibody would be less likely, reducing cell activation and urticaria/angioedema.
Objective: To investigate the efficacy of omalizumab in patients with CAU symptomatic despite antihistamine therapy.
Methods: Twelve patients with CAU, identified by basophil histamine release assay and autologous skin test, with persistent symptoms for at least 6 weeks despite antihistamines, were treated with placebo for 4 weeks followed by omalizumab (≥0.016mg/kg/IU mL^{-1} IgE per month) every 2 or 4 weeks for 16 weeks. Primary efficacy variable was change from baseline to the final 4 weeks of omalizumab treatment in mean Urticaria Activity Score (UAS, 0-9 scale). Changes in rescue medication use and quality of life were assessed.
Results: Mean UAS declined significantly from baseline to the final 4 weeks of omalizumab treatment (7.50 ± 1.78 to 2.66 ± 3.31, -4.84 ± 2.86, P = .0002). Seven patients achieved complete symptom resolution. In 4 patients, mean UAS decreased, but urticaria persisted. One patient did not respond. Rescue medication use was reduced significantly, and quality of life improved. No adverse effects were reported or observed.
Conclusion: This exploratory proof of concept study suggests omalizumab is an effective therapy for CAU resistant to antihistamines. (J Allergy Clin Immunol 2008;122:569-73.)

Key words: *Chronic urticaria, angioedema, autoantibody, omalizumab, IgE receptor, antihistamines*

Abbreviations used
CAU: Chronic autoimmune urticaria
DLQI: Dermatology Life Quality Index
UAS: Urticaria Activity Score

Chronic urticaria is thought to have an autoimmune basis in approximately 45% of patients. The most common association is the presence of IgG antibody directed to the α-subunit of the IgE receptor. This autoantibody cross-links the α-subunits, leading to degranulation of basophils[1,2] and cutaneous mast cells.[3] Histamine can be readily detected in basophil release assays, which use patient serum, or purified IgG, or IgG subclasses[4] isolated by affinity chromatography. Histamine release is augmented by complement activation[2] with release of C5a.[5] There is also evidence for basophil secretion of leukotrienes and cytokines. The chemotactic activity of C5a for neutrophils, eosinophils, and monocytes[6] is consistent with the prominence of these cells in skin biopsies of chronic urticaria[7,8] compared with the infiltrate seen in allergic late-phase reactions. Associated autoimmune phenomena include a 25% incidence of antithyroid antibodies, which can result in Hashimoto thyroiditis,[9-11] as well as positive antinuclear antibodies (A. P. Kaplan, unpublished data, September 2008). More rarely, patients may present with Graves disease, type I diabetes mellitus, and vitiligo. The mainstays of initial therapy include antihistamines with the possible addition of H2-blockers and leukotriene pathway inhibitors. Systemic corticosteroids or cyclosporine are frequently used in the treatment of refractory disease[12]; however, vigilance regarding potential side effects is required when these agents are used.

Omalizumab is a recombinant humanized mAb that selectively binds to IgE. Omalizumab inhibits the binding of IgE to the high-affinity IgE receptor (FcεRI) on the surface of mast cells and basophils and reduces the number of FcεRI receptors on basophils in atopic patients.[13,14] We postulated that in patients with chronic autoimmune urticaria (CAU), omalizumab would effect a sufficient reduction in FcεRI expression to prevent IgG antibody-mediated cross-linking of adjacent α-subunits and thereby prevent cellular activation. Our experience with 12 such patients is described herein.

METHODS

At a screening visit, patients age 18 to 75 years had a complete history and physical examination, laboratory evaluations, electrocardiogram, and clinical assessment of urticaria and angioedema. Patients with chronic urticaria were defined as having symptoms for at least 6 weeks, with hives present most days of the week despite antihistamines. A total serum IgE ≤700 IU/mL was required to enter the study. Postulating that even small amounts of IgE might affect FcεRI density, there was no minimal level of IgE required for entry. Patients provided serum for an assay of basophil histamine release[2,4] and underwent an autologous skin test.[1,15] A positive test for either was sufficient to

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TABLE I. Scoring system for urticaria severity

Score	Pruritus severity	No. of hives	Size of largest hive (cm)	Interference with sleep	Interference with daily activities	Erythema severity
0	None	None	None	None	None	None
1	Mild, minimal awareness, easily tolerated	1-6	<1.25	Mild, not troublesome, adequate sleep	Mild, not troublesome, little effect on activity	Slight
2	Moderate, definite awareness, bothersome but tolerable	7-12	1.25-2.5	Moderate, awoke occasionally, average sleep	Moderate, some interference with activity	Moderate
3	Severe, difficult totolerate	>12	>2.5	Severe, substantial interference with sleep, poor sleep	Severe, daily activities substantially or completely curtailed	Significant

TABLE II. Patient characteristics

Patient no.	Age (y)	Sex	Duration of symptoms (continuous)	Total serum IgE (IU/mL)	Thyroid antibodies	Baseline UAS (0-9)
1	34	F	11 mo	102	Negative	8
2	53	F	30 y	81	(*) Negative	9
3	62	M	2.5 y	39	(+) Antiperoxidase (824)	9
4	39	M	3 y	59	Negative	8
5	38	M	12 y	10	Negative	8
6	59	M	1 y	18	(+) Antiperoxidase (54)	9
7	41	F	6 mo	2	Negative	9
8	34	F	7 wk	22	(+) Antiperoxidase (250)	9
9	64	F	18 y	44	(+) Antiperoxidase (50)	9
10	32	F	7.5 y	69	(+) Antithyroglobulin (41)	9
11	52	F	3 mo	26	Negative	9
12	59	F	4 mo	4	Negative	9

F, Female; *M,* male.
(*) History of Hashimoto thyroiditis, although autoantibodies were negative.
(+) Positive, titer shown in parentheses.

be included in the study. A 1-week screening period was used to establish patient eligibility further. All patients maintained a daily diary to record urticaria signs and symptoms based on a scoring system (0-3) as shown in Table I. Pruritus severity had to be at least moderate (score of 2 on a 0-3 scale), and the Urticaria Activity Score (UAS), a combination of pruritus severity, number of hives, and size of largest hive, had to be at least moderate (minimum score of 4 on a 0-9 scale). The presence or absence of angioedema and its location and duration were noted. Exclusion criteria were physical urticaria, urticarial vasculitis, or urticaria secondary to any underlying disease or allergic reactions to foods or drugs. Patients who had taken oral or parenteral corticosteroids, methotrexate, cyclosporine, or other immunosuppressant medications during the 4 weeks before screening were also excluded.

After inclusion criteria were met, all medications for the treatment of urticaria were discontinued. All patients received placebo for 4 weeks and then omalizumab for 16 weeks. Patients were blind to treatment sequence. Omalizumab was administered consistent with the US product label every 2 weeks or every 4 weeks, dosed according to the patient's body weight, and serum IgE obtained at the screening visit. Patients with IgE <30 IU/mL received 150 mg omalizumab every 4 weeks. Daily diaries for urticaria signs and symptoms were maintained throughout the study. At monthly visits, the mean UAS was calculated, rescue medication use was tabulated, and the Dermatology Life Quality Index (DLQI) questionnaire was administered.[16] Also at each monthly visit, an overall therapeutic response was determined by the investigator on a 5-item scale (1-5) with 1 representing complete relief; 5 represented no change or worsening in signs and symptoms; 2,3, and 4 represented marked, moderate, or slight relief, respectively. At the final study visit, serum was obtained for a posttreatment assay of basophil histamine release, and an autologous serum skin test was again administered. Patients who exhibited angioedema at randomization were reassessed for its presence.

Patients were permitted to take 25 to 50 mg hydroxyzine as often as 4 times a day as needed throughout the study. The use of hydroxyzine was tabulated at each study visit. In the case of severe symptoms, oral corticosteroid could be added at the discretion of the investigator.

The protocol for the study was approved by the Institutional Review Board of National Allergy, Asthma, and Urticaria Centers of Charleston, and informed consent was obtained in writing from the participants.

Histamine release from basophils and histamine assay

One healthy blood donor whose cells were reactive with anti-IgE antibody and known to be responsive to patient sera[2] was chosen for this study. This donor is atopic with a serum IgE level of 25 IU/mL. Seventy-five microliters of serum, buffer, or positive controls (antihuman IgE 1 mg/mL) was incubated with 75 μL leukocyte suspension for 40 minutes at 37°C. After incubation, the supernatants were separated by centrifugation at 1500 rpm for 5 minutes at room temperature. Two replicate aliquots of cells were boiled to determine total basophil histamine content. The concentration of histamine in the supernatant and the total basophil histamine content were measured with an enzyme immunoassay (Beckman Coulter, Fullerton, Calif), according to the manufacturer's instructions. Histamine release was expressed as a percentage of total histamine content. Spontaneous histamine release from the cell suspension was less than 5% of total histamine. A level of 15% or more was taken as positive.[2] The final assay repeated the samples obtained at entry with the determination at the end of the study so that they were assayed together with the same basophil preparation.

Statistical analysis

The primary efficacy variable was the change from baseline in mean UAS (ie, the average over the 4-week placebo treatment period) to the final 4-week period of omalizumab treatment. Secondary efficacy variables included the

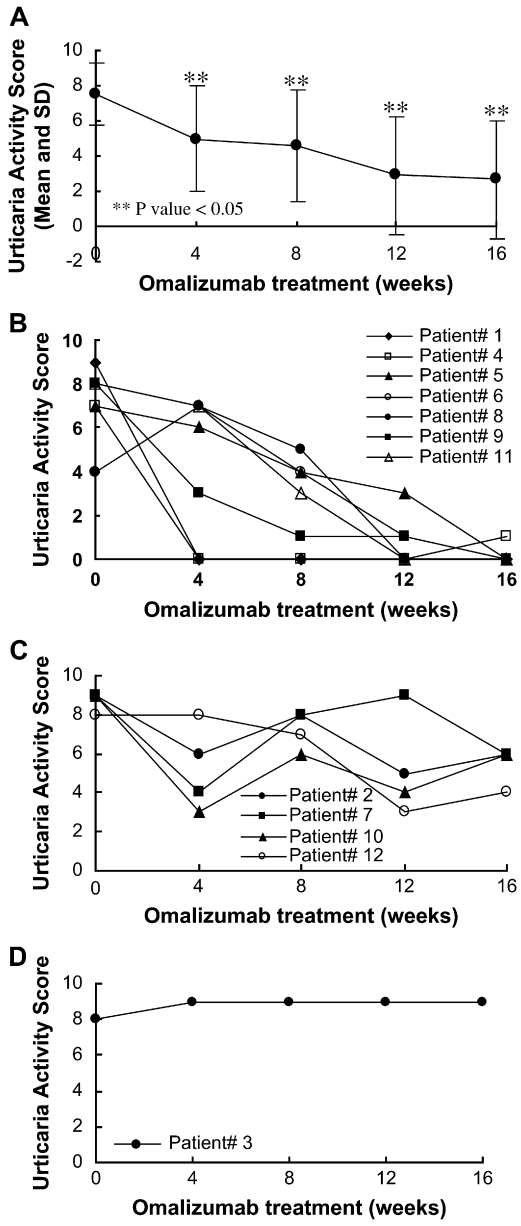

FIG 1. UASs of 12 patients with chronic autoimmune urticaria treated with omalizumab for 16 weeks. **A,** Means and SDs of UASs of all 12 patients. Statistically significant decrements in symptom scores were observed at weeks 4, 8, 12, and 16. **B,** The response of 7 patients with complete resolution of symptoms. **C,** The response of 4 patients who had a partial improvement in symptoms. **D,** Single patient with no response.

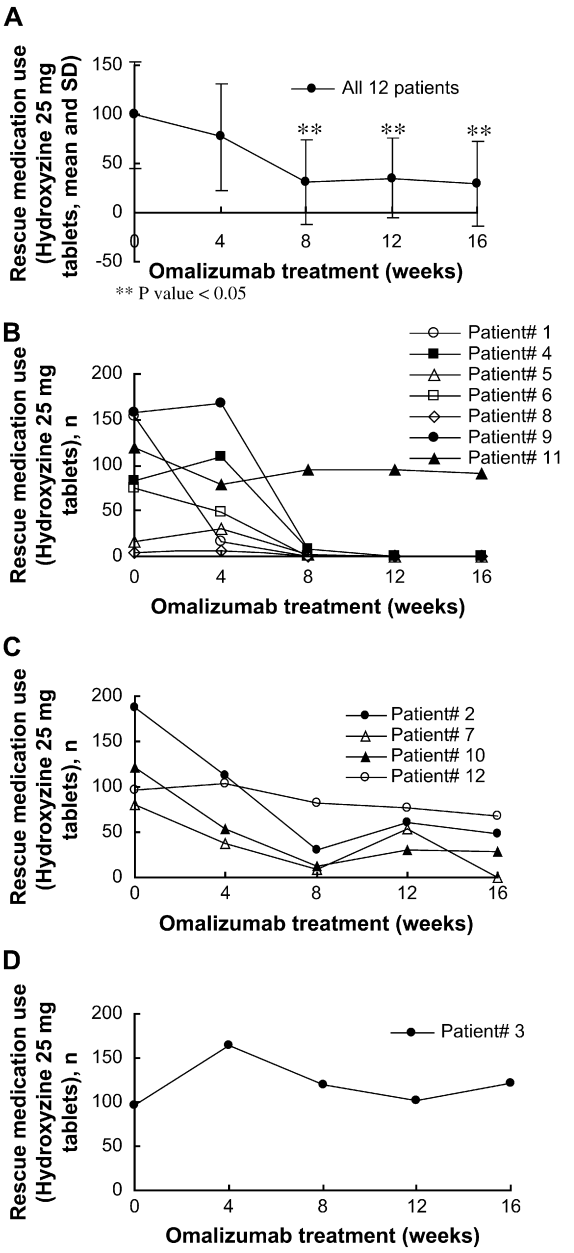

FIG 2. The use of hydroxyzine by 12 patients with chronic urticaria treated with omalizumab. Hydroxyzine was taken on an as-needed basis for a 20-week period by the study patients. **A,** Means and SDs of the use of hydroxyzine by all 12 patients. **B,** Patients with a marked response. **C,** Patients with partial response showing progressively less use of drug in most instances. **D,** The patient with no response.

percentage of responders (ie, the proportion demonstrating a change from baseline in mean UAS of $\geq$50%), and change from baseline in interference with sleep, interference with daily activities, overall therapeutic response, rescue medication use, and DLQI. Statistical analyses were performed using paired *t* tests. A *P* value of <.05 was considered significant. No adjustment was made for multiplicity.

RESULTS

Study subjects had daily urticaria for periods ranging from 7 weeks to 30 years. None had a satisfactory response to maximal dose antihistamine therapy. Their baseline characteristics are given in Table II. All patients had a positive histamine release assay; 8 had a positive autologous skin test result, 3 had a negative skin test result, and 1 test was not performed. None of the patients had allergic asthma that would otherwise qualify them for treatment with omalizumab.

Mean UAS declined significantly from baseline to the final 4-week period of omalizumab treatment (7.50 $\pm$ 1.78 to 2.66 $\pm$ 3.31; change in mean UAS, –4.84 $\pm$ 2.86; $P = .0002$; Fig 1, *A*). A statistically significant reduction was observed by week 4, and mean UAS scores continued to decline through week 16. On an individual patient level, 7 patients achieved complete resolution of symptoms (Fig 1, *B*). Four patients experienced a reduction

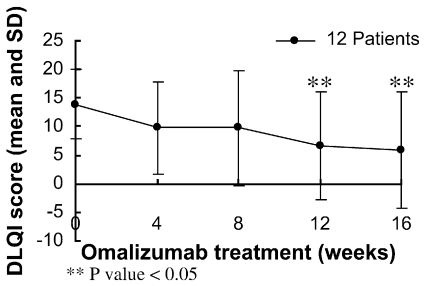

FIG 3. Quality of life scores of patients with chronic urticaria treated with omalizumab for 16 weeks. Means and SDs of quality of life scores assessed at the time of each visit.

in mean UAS, but urticaria persisted (Fig 1, *C*). One patient was a nonresponder (Fig 1, *D*). Eight of 12 patients experienced at least a 50% reduction in mean UAS. Significant improvement from baseline in interference with sleep, interference with daily activities, and overall therapeutic response was observed and paralleled the reduction in mean UAS.

Treatment with omalizumab resulted in a significant decrease in mean rescue medication use from 99.3 (±54.1) tablets at baseline to 29.8 (±42.9) tablets during the final 4-week period of omalizumab treatment (change in mean rescue medication use, –69.5 ± 60.5; $P = .004$; Fig 2, *A*). Six of the 7 complete responders took no hydroxyzine after week 12 (Fig 2, *B*). The seventh continued to take rescue medication because of a misunderstanding regarding as-needed use. There was a marked reduction in hydroxyzine use in the 4 patients who responded partially (Fig 2, *C*) and no change in the patient who did not respond (Fig 2, *D*).

The DLQI questionnaire revealed improvement in mean total quality of life score (Fig 3) for all patients taken as a sum of their scores. The 1 nonresponder exacerbated severely at week 8 and was placed on oral prednisone 4 to 10 mg/d for the remainder of the study. To reflect this treatment failure, the maximum score of 3 was assigned to all of this patient's subsequent responses.

The histamine release assay was initially positive in all patients (Table III). After treatment, the assay reverted to negative in 4 of the 7 patients who responded completely and 1 of the 4 patients who improved. It remained positive in 3 patients who responded completely, 2 who improved, and the 1 nonresponder. A posttreatment sample was not obtained from 1 patient (improved).

No adverse events were reported or observed.

DISCUSSION

Chronic urticaria is a disease that is particularly difficult to treat, and in severe cases, the functional impairment associated with it is similar to that seen with coronary artery disease.[17,18] Although nonsedating antihistamines are recommended as first-line agents, a substantial proportion of patients remain poorly responsive to these agents even if H2-receptor antagonists and/or leukotriene pathway inhibitors are added.[19] Such patients are often treated with corticosteroids[12] or cyclosporine,[20,21] and alternatives to these agents would be a welcome addition if efficacy could be shown with an acceptable tolerability profile.

One major subpopulation of patients with chronic urticaria is thought to have an autoimmune etiology (40% to 45%) in which there is IgG antibody directed to the α-subunit of the high-affinity IgE receptor (35% to 40%)[19] or to IgE itself (IgG anti-IgE; 5% to 10%).[22] As a group, symptoms are more severe in this subpopulation of patients than in patients without such autoantibodies.[23] These autoantibodies can be demonstrated by basophil histamine release assay or by autologous skin testing. Cross-linking IgE receptors or adjacent IgE molecules by these antibodies is requisite for activation to occur,[24] and complement, especially C5a,[5] augments the reaction. We reasoned that omalizumab, by decreasing circulating IgE levels, will secondarily decrease the IgE receptor density on basophils and cutaneous mast cells, preventing activation by autoantibodies. In addition, omalizumab has been reported to ameliorate the symptoms of chronic urticaria in an uncontrolled study of 3 patients, 2 of whom also had IgE-mediated asthma.[25]

In this study, mean UAS decreased, mean rescue medication use declined, and overall therapeutic response and quality of life improved. This consistency in effect across all defined outcome measures demonstrates the internal validity of the study and suggests omalizumab may be useful in the treatment of patients with CAU not responsive to antihistamines.

Although no patient had asthma, the dose and dosing frequency were based on the total serum IgE and body weight, consistent with that used for asthma patients otherwise eligible for omalizumab therapy. Patients with IgE <30 IU/mL received the lowest dose of omalizumab stipulated in the product label. A post hoc analysis revealed that 5 of 6 patients with a baseline total serum IgE <30 IU/mL responded, and 3 of 6 patients with an IgE ≥30 IU/mL responded. This suggests that eliminating even small amounts of IgE may modulate the disease process.

The limitations of this study were that it involved a small cohort of patients and was not a parallel-group, placebo-controlled trial, which may not have taken into account the potential cyclical nature of the disease in some. Although patients were blind to treatment sequence, investigators were aware. Among its strengths are a careful characterization of patients entering the trial, assessment of effect after placebo exposure to establish a baseline, and close follow-up based on specialist care. Most importantly, outcome measures were primarily patient-reported, enhancing the external validity of the study.

Although patients were eligible for enrollment on the basis of either a positive test for anti-IgE receptor antibody by histamine release assay[26] or by autologous skin test,[27] all patients were initially positive for basophil histamine release. The assay is considered to be the most reliable test to categorize patients into the autoimmune versus idiopathic subgroups.[26] The favorable result observed, presumably secondary to downregulation of the high-affinity IgE receptor, may represent the first time an immune modulator has been observed to downregulate this autoimmune target. Although omalizumab downregulates IgE receptors on patients' basophils or mast cells,[28] it should not affect the level of an IgG autoantibody directed against IgE receptor. Nevertheless, as demonstrated by the repeat of the basophil histamine release assay at study end (Table III), there was a decrease in functional antibody in 5 patients who had complete clearing of hives and in 3 patients who experienced a reduction in symptoms. It is not possible to distinguish whether reducing antigen load might have an effect on antibody levels or whether some of these represent spontaneous remissions. However, as a consequence of lowering serum IgE levels, the lowering of FcεRI on basophils and mast cells for 16 weeks may have provided negative feedback to production of functional autoimmune IgG antibodies. Only further observation will determine whether downregulation of the target antigen structure for a period results in continued remission of CAU either through

TABLE III. Functional antibody to the IgE receptor (or IgE) assayed by basophil histamine release

Patient no.	Percent histamine release* (screen)	Percent histamine release (after treatment)	Urticaria symptoms (after treatment)
1	57.4	13.3	Complete resolution
2	97.9	32.0	Improved
3	18.1	100	Nonresponder
4	100	0	Complete resolution
5	19.1	20.5	Complete resolution
6	28.2	8.3	Complete resolution
7	24.0	16.2	Improved
8	80.3	11.9	Complete resolution
9	27.7	40.3	Complete resolution
10†	89.1	—	Improved
11	100	25.8	Complete resolution
12	43.7	12.2	Improved

*Normal is less than 15%.
†Posttreatment sample not obtained.

long-term suppression of autoantibody production, or repopulation of FcεRI, which is recognized as "self" by the immune system.

At baseline, 8 subjects had a positive autologous skin test result, 3 had a negative test, and 1 test was not performed. Test results remained positive in 3 patients who remitted and whose histamine release assay turned negative. The serum factors responsible are not clear because no serum fractionation has been performed to ascertain the molecular species responsible. Thus, it is possible that factors other than IgG anti-FcεRI (eg, immunoglobulin of other classes or alternative antibodies) may be responsible for positive skin test results. It is also possible that compared with circulating basophils used in the histamine release assay, there is a slower turnover of FcεRI on tissue resident cells.

Future studies should include a larger number of patients and have a double-blind placebo-controlled design. In addition, studies of patients without associated autoimmune phenomena should be conducted to determine whether the findings reported here can be extended to the larger population of patients with chronic urticaria that is not thought to be autoimmune in nature.

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Clinical implications: Omalizumab may be useful for treatment of patients with CAU not responsive to antihistamines. Further studies should be performed to confirm these findings in CAU and to assess efficacy in other forms of chronic urticaria.

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