

Original Investigation

Retreatment With Omalizumab Results in Rapid Remission in Chronic Spontaneous and Inducible Urticaria

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IMPORTANCE Omalizumab has emerged as a novel and effective treatment option for patients with antihistamine-resistant chronic urticaria. It is unclear whether patients with recurrent urticaria symptoms after discontinuation of omalizumab treatment can benefit from retreatment.

OBJECTIVE To assess the response of patients with chronic urticaria who receive omalizumab retreatment.

DESIGN, SETTING, AND PARTICIPANTS Retrospective analyses were conducted of outpatients treated at an urticaria specialist center of a university hospital. Participants included 25 consecutive patients (aged 18-74 years; 18 women) with chronic spontaneous urticaria, chronic inducible urticaria, or both who showed complete response to omalizumab treatment, experienced relapse after discontinuation of treatment, and received retreatment with omalizumab.

INTERVENTIONS Subcutaneous treatment with omalizumab (150-600 mg/mo).

MAIN OUTCOMES AND MEASURES Response after retreatment was assessed by the urticaria activity score in patients with chronic spontaneous urticaria and by trigger threshold testing (in patients with cold urticaria or symptomatic dermographism) and/or a carefully determined history (in patients with cholinergic urticaria, solar urticaria, or pressure urticaria). Adverse events were documented.

RESULTS All patients experienced complete response after retreatment. None of the patients reported relevant adverse events during omalizumab treatment and retreatment.

CONCLUSIONS AND RELEVANCE Omalizumab retreatment is effective and safe in patients with chronic urticaria who have benefited from initial omalizumab treatment.

JAMA Dermatol. 2014;150(3):288-290. doi:10.1001/jamadermatol.2013.8705
Published online January 29, 2014.

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Treatment of chronic urticaria is difficult because many patients are refractory to conventional therapy. Recently, omalizumab, an anti-IgE antibody approved for the treatment of moderate to severe asthma, has emerged as an effective, guideline-recommended treatment option for patients with antihistamine-resistant chronic urticaria.¹⁻⁵ As of now, more than 1000 patients with chronic spontaneous urticaria (CSU) have reportedly^{1-4,6-12} been treated with omalizumab, many in clinical trials. Most study patients who achieved benefit from this treatment experienced relapse of symptoms after completion of the clinical trial in which they were enrolled (ie, after cessation of omalizumab treatment).⁶ In patients with urticaria treated with omalizumab outside of clinical trials, the drug is used off-label. Off-label omalizumab treatment is frequently limited to a trial of a few months'

duration. Because of this, most patients who have benefited from omalizumab, within or outside of clinical trials, and have experienced relapse of symptoms after cessation of treatment are considered for retreatment with omalizumab. To our knowledge, there have been no reports on the effects, response rates, and adverse events in patients with chronic urticaria retreated with omalizumab.

Methods

Patients

We retrospectively assessed disease activity and adverse events in 25 patients with CSU and/or chronic inducible urticaria (aged 18-74 years; 18 women) who received omalizumab

retreatment after a successful trial of this drug (ie, $\geq 90\%$ improvement of symptoms without the need for concurrent use of antihistamines) after first treatment with omalizumab and relapse of the symptoms. The patients received treatment at the urticaria specialist clinic of the Department of Dermatology, Venerology, and Allergology, Charité-Universitätsmedizin Berlin. In all patients receiving omalizumab, successful applications for funding by health insurers were necessary so that the patients did not have to meet the costs of treatment. Because these analyses were conducted on data recorded during the routine care of patients, approval by our ethics committee was not required and no formal inclusion or exclusion criteria were applied; the only exclusion criterion was that patients who were participating in clinical trials were not included.

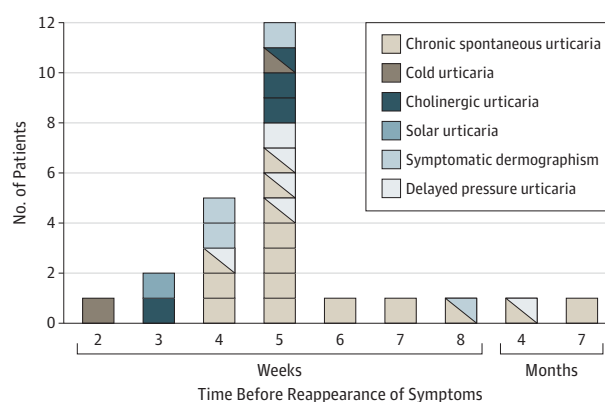
Treatment

All patients received initial treatment for at least 3 months with omalizumab doses ranging from 150 to 600 mg/mo given subcutaneously in 2- to 4-week intervals. In some patients, the doses were increased to achieve complete symptom control; in others, doses were decreased or the interval between doses was prolonged.⁷ Disease activity in patients with CSU was determined before and after initial treatment with omalizumab by use of the Urticaria Activity Score 7,¹³ and a reduction of 90% or more was considered to indicate complete response. Urticaria activity scores were calculated based on patients' daily documentation of symptoms in diaries. Disease activity in patients with inducible urticaria was determined by trigger threshold testing (in patients with cold urticaria or symptomatic dermographism) and/or by the patient's history (in patients with cholinergic urticaria, solar urticaria, or pressure urticaria). A reduction of the trigger strength by 90% or more was considered complete response. Retreatment was initiated after the recurrence of symptoms without prior monitoring of disease activity. All patients received the same dose of omalizumab in the same interval as the last successful treatment before discontinuation of treatment. Adverse events were documented during follow-up visits (every 2-4 weeks).

Results

Overall, 25 patients, with a mean age of 45 years (range, 18-74 years; 18 women [72%] and 7 men [28%]) with chronic urticaria (9 [36%] CSU, 5 [20%] CSU and delayed pressure urticaria, 3 [12%] cholinergic urticaria, 3 [12%] symptomatic dermographism, 1 [4%] delayed pressure urticaria, 1 [4%] solar urticaria, 1 [4%] cold urticaria, 1 [4%] CSU and symptomatic dermographism, and 1 [4%] cold urticaria and cholinergic urticaria) were included in this retrospective analysis. All patients had complete symptom control (defined as $\geq 90\%$ improvement) without the requirement of any other drugs used for treatment of urticaria after their first use of omalizumab. All of the patients experienced a relapse of disease resulting in urticaria symptoms despite antihistamine treatment within 2 to 8 weeks after their last omalizumab injection, except for

Figure. Time to Urticaria Relapse After Omalizumab Treatment



Each patient is represented by a square, with colors indicating the type of urticaria disease. Two colors within a single square indicate comorbidity of 2 urticaria diseases.

2 patients (8%) who experienced relapse after 4 and 7 months. On reinitiation of omalizumab treatment, all patients reported a rapid and complete response after the first injection within the first 4 weeks, usually during the first days, of re-treatment (Figure). All patients were able to stop antihistamine treatment, and none reported relevant adverse events (ie, adverse effects other than mild and transient injection site reactions) during the initial use or during the second round of treatment.

Discussion

To our knowledge, this is the first report that retreatment with omalizumab can be effective and safe in patients with chronic urticaria who had previously benefited from this treatment. Notably, all patients showed the same response rate (100%) and relevant adverse event rate (0%) on retreatment as they did during their first trial of omalizumab.

This was a retrospective analysis of data from the medical records of 25 individuals. It has strength in that it reflects an important clinical situation faced in urticaria therapy. It also, by its nature, has weaknesses, which include the small number of patients and the lack of information about the comparative times of onset of the first and second responses.

The patients included in these analyses had to fulfill 2 selection criteria. First, they had to show complete response ($\geq 90\%$ improvement of symptoms) to their first treatment of omalizumab. Second, they had to demonstrate relapse after discontinuation of omalizumab treatment. Both benefit from omalizumab and relapse after its discontinuation is the rule, and not the exception, in patients with chronic urticaria that we treat. Less than 30% of all our patients with urticaria who receive omalizumab outside of clinical trials show no response or only partial response to omalizumab treatment,⁷ and less than 10% of the patients who respond remain free of symptoms after discontinuation of omalizumab therapy. Thus, the question whether chronic urticaria should be retreated with

omalizumab arises frequently and, most often, in patients who have previously received this drug.

Omalizumab doses required to achieve complete response varied widely among patients (from 150 to 600 mg/mo). In individual patients, however, the doses that resulted in complete protection after retreatment were the same as those that did so during initial treatment, indicating that patients exhibit distinct and persistent levels of response. Similarly, the dosing schedule varied among patients. However, in most of our patients who receive omalizumab, a 4-week interval between injections has been optimal.⁷

We did not check the patients who received omalizumab for the development of neutralizing antibodies, and our results do not support a need to do so. Previous analyses¹⁴ of

patients with asthma or allergic rhinitis demonstrated that omalizumab treatment does not lead to measurable anti-omalizumab antibodies in these patients, and our data do not suggest that patients with urticaria are any different.

Conclusions

Although the number of patients observed here is too low to draw definite conclusions, our findings strongly suggest that retreatment with omalizumab is a safe and effective option for treatment of chronic urticaria in patients who previously benefited from this drug and show relapse of symptoms.

ARTICLE INFORMATION

Accepted for Publication: September 14, 2013.

Published Online: January 29, 2014.

doi:10.1001/jamadermatol.2013.8705.

Author Contributions: Drs Metz and Maurer had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Metz, Maurer.

Acquisition of data: Ohanyan, Maurer.

Analysis and interpretation of data: All authors.

Drafting of the manuscript: Metz, Church, Maurer.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Church.

Administrative, technical, or material support:

Ohanyan, Maurer.

Study supervision: Metz, Maurer.

Conflict of Interest Disclosures: Dr Metz received honoraria from Bayer, Novartis, UCB, and Dr R. Pflieger. Dr Church has been a speaker or consultant for Almirall, FAES Menarini, MSD, Pharma, UCB Pharma, sanofi-aventis, and Uriach. Dr Maurer is a speaker and/or advisor for Almirall, Bayer, Biofrontera, FAES, Genentech, GSK, Merckle Recordati, MSD, Moxie, Novartis, sanofi-aventis, UCB, and Uriach. No other disclosures were reported.

Additional Contributions: Hesna Gözlükaya provided excellent technical and medical assistance. Gözlükaya received no financial compensation for these services.

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