



Letter

Positive response to omalizumab in patients with acquired idiopathic nonhistaminergic angioedema

Angioedema is defined as a localized and self-limiting subcutaneous and submucosal tissue edema due to a short-term release of vasoactive mediators, causing an increase in vascular permeability. Although most often accompanied by hives, angioedema may appear isolated and, like urticaria, display a chronic outcome with repeated outbreaks and no objective identifiable cause.¹

A recent consensus on the classification, diagnosis, and treatment of angioedema divided the acquired-type angioedema of unknown cause into histaminergic and nonhistaminergic, according to antihistamines response. For nonhistaminergic angioedema (corresponding to the so-called bradykinergic² until recently), the most common treatment is tranexamic acid.²

Omalizumab is a recombinant humanized monoclonal anti-IgE antibody. It is the first monoclonal antibody approved for patients with chronic spontaneous urticaria nonresponsive to antihistamines and for severe allergic asthma. Its mechanism of action is not completely understood. It lowers IgE levels toward zero, down-regulating IgE receptors, and seems to desensitize mast cells.³ We report our results with omalizumab in a series of patients with acquired idiopathic nonhistaminergic angioedema.

Eight patients were studied. Their characteristics are given in Table 1. We ruled out all underlying diseases, such as hereditary angioedema (normal function and C1 inhibitor esterase levels), acquired deficiency of C1 inhibitor, or use of angiotensin-converting enzyme inhibitor drugs. Clinical course was prolonged in all cases, several years in most, with a significant degree of severity as indicated by visual analog scales and angioedema activity scores.⁴ No response to antihistamines was observed in any patient even at the 4-fold dose; thus, angioedema was labeled as idiopathic nonhistaminergic angioedema. Frequent exacerbations required corticosteroid use (methylprednisolone, 40–60 mg/d for 1–2 days), with a quick and favorable response in most patients. The fact that most of the patients had a good response to corticosteroids in the acute phase suggests that bradykinin would not be an essential mediator in this type of patients. However, no long-term prophylaxis corticosteroids were prescribed to prevent their deleterious adverse effects, and omalizumab as compassionate use was offered to all patients. Before this step, 2 patients who were taking tranexamic acid, shortly withdrawn in both of them because of lack of response, had an increase in liver enzymes. In another patient, tranexamic acid was contraindicated because of a recent stroke.

We started with an initial monthly dose of 300 mg, and once symptoms stabilized, the dose and/or frequency of administration was reduced to the minimum required for symptom control (no angioedema attacks). As indicated in Table 1, some patients' conditions were controlled with doses as low as 75 mg, with wide time

ranges from 3 to 16 weeks (eTables 1 and 2). The response to omalizumab was immediate in all cases on omalizumab administration, ranging from 2 to 14 days. After remission of symptoms for a long period (6 months to 1 year), omalizumab was withdrawn in 6 patients. Only 1 patient remained asymptomatic, and treatment had to be restarted in the rest of patients because of relapsing outbreaks of angioedema with a similar response than the one achieved with the first treatment. Again, complete remission was achieved within a few days after restarting omalizumab treatment. No adverse effects attributable to the drug were observed in any case.

Several recent studies, with proper designs and large sample sizes, have documented the efficacy of omalizumab in chronic spontaneous urticaria,^{5,6} as well as in isolated cases in other types of chronic urticaria.⁷ In clinical trials, part of the included patients had associated angioedema, but the effect of omalizumab focused on parameters related to pruritus and urticaria activity, such as the Itch Severity Score and the 1-week Urticaria Activity Score, and not on the response of angioedema. The first report on the benefit of omalizumab in recurrent idiopathic angioedema was by Sands et al⁸ in 2007. They found an excellent response in 3 patients with severe angioedema after omalizumab doses between 300 mg every 4 weeks and 375 mg every 2 weeks. The improvement was immediate, as in our cases, and follow-up time ranged from 7 to 21 months; in 2 of 3 cases, omalizumab was prescribed because of an associated asthma. Recently, 2 more reports on isolated cases found a good response to 300 mg of omalizumab every 4 weeks.^{9,10}

Table 1
Clinical and demographic characteristics

Characteristic	Findings ^a
No. of patients	8
Male sex	5 (62)
Age, mean (range), y ^a	54 (34–70)
IgE, mean (range), IU/mL ^a	121 (44–402)
Evolution time, mean (range), y ^a	7 (2–14)
Evolution time, y	
0–5	2
5–10	4
>10	2
No. of outbreaks per month, mean (range)	5 (1–12)
VAS score before treatment, mean (range)	8.25 (7–10/10)
AAS before treatment, mean (range)	168 (45–420)
Omalizumab, mean (range)	
Dose	150 (75–300)
Frequency, wk	8 (3–16)
Duration, y	2.25 (1–3)
VAS score after treatment	0
AAS after treatment	0

Abbreviations: AAS, angioedema activity score; VAS, visual analog scale.

^aData are presented as number (percentage) of patients unless otherwise indicated.

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The mechanism of action for benefit in urticaria and angioedema is not fully understood at the moment. The rapid response that may occur in several days is too fast to be explained on the basis of receptor down-regulation, although such an effect may participate in upholding benefit.

In conclusion, we report the largest series studied to date of patients with severe idiopathic nonhistaminergic angioedema treated with omalizumab with a long follow-up period, revealing an exceptional response. The response is almost immediate, with a dose interval required that varied greatly from patient to patient. Discontinuation leads to recurrence of symptoms in almost all cases, with a good response on retreatment. Although more controlled studies are needed, including a larger number of patients, omalizumab is a beneficial treatment for these patients, with a high safety profile.

Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2015.02.007>.

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eTable 1

AASs before and after treatment

Patient No.	AAS before treatment	AAS after treatment
1	96	0
2	252	0
3	200	0
4	49	0
5	420	0
6	98	0
7	182	0
8	45	0

Abbreviation: AAS, angioedema activity score.

eTable 2Individual treatment regimens and responses^a

Patient No.	Dose	Interval, wk
1	150	4
2	75	4
3	75	3
4	150	8
5	150	8
6	150	16
7	150	8
8	300	12

^aAll patients had an exceptional response.