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Omalizumab also successful in chronic urticaria

To the Editor:

We read with interest "Successful treatment of 3 patients with recurrent idiopathic angioedema with omalizumab."¹

We recently reported on 3 patients with refractory chronic urticaria who had marked improvement with omalizumab.² Two of the patients showed evidence of elevated anti-FcεRI antibodies, whereas 1 did not. We postulated that the possible mechanisms included the downregulation of IgE receptors providing fewer targets for IgE or anti-FcεRI antibodies.

In discussion of possible mechanisms, the authors indicate that the cases "do not appear to be IgE-mediated events." However, patients 1 and 2 had elevated IgE (244 and 510, respectively). The assay used to detect anti-FcεRI antibodies was not mentioned, but current commercial assays can be associated with false-negatives. The autologous serum skin test can similarly be false-negative. A basophil histamine release test, in which patient serum is incubated with donor basophils, was not performed but would be a useful indication of the presence of autoantibodies if positive.

It is also suggested by the authors that the apparent rapid improvement suggests a non-IgE-mediated mechanism because "omalizumab effects in asthma and allergic rhinitis occur in 8 to 10 weeks concomitant with reduction of bound IgE and IgE receptors and not with the initial reduction in free IgE levels." On the contrary, many omalizumab studies have correlated clinical improvement with reduction in free IgE levels within 4 weeks.^{3,4} In our report, 2 patients responded with clearing of urticaria within 1 week and 1 patient within 6 weeks. Aside from the mechanisms of binding of free IgE and downregulation of IgE receptors attributed to omalizumab, an effect on mast cell and basophil survival may be involved.⁵

It is not mentioned how long after stopping lisinopril omalizumab was started. Angiotensin-converting enzyme inhibitor-induced angioedema can persist for a period after cessation of the drug, making it possible for spontaneous resolution to have occurred after omalizumab was initiated.

Finally, one of our patients had low serum IgE level (<9 IU/mL), so we agree with the possibility of a non-IgE-mediated mechanism of action for omalizumab brought up by the authors.

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Reply

To the Editor:

We appreciate the correspondence from Spector and Tan¹ regarding our article on treatment of recurrent idiopathic angioedema with omalizumab.² We note their report on omalizumab use in chronic refractory urticaria.³

There are several common threads in both articles. The mechanisms driving neither idiopathic urticaria nor idiopathic angioedema are fully elucidated. Omalizumab, having apparent efficacy in both short series, demonstrates potential as a new therapeutic agent pending results of controlled trials. One might infer, therefore, that these partially overlapping syndromes, responding to similar treatment, might share underlying mechanisms. However, neither case series is designed to address mechanisms, so comments about mechanism in either group of patients remain highly speculative. Stated differently, some or none of the 6 patients described in either study might have responded to omalizumab because of IgE-mediated mechanisms.

We take issue with the implication by Spector and Tan¹ that the presence of elevated serum IgE levels in 2 of 3 patients with angioedema carries much predictive weight mechanistically. Total serum IgE levels have limited diagnostic utility because of considerable overlap in normal and atopic populations.⁴ Even in the urticaria series by Spector and Tan,³ 1 of 3 patients had a normal IgE level. We agree that for prospective studies, a panel of tests for antibodies directed against FcεRI, *in vitro* basophil histamine release, and possibly the autologous serum skin test would be appropriate, fully recognizing that the sensitivity and specificity of these tests are less than ideal in urticaria, let alone angioedema.^{5,6} We used a commercially available functional FcεRI antibody assay.

We concede that some asthma and rhinitis studies of omalizumab demonstrated efficacy as early as 4 weeks after initial dosing.^{7,8} We reiterate that IgE and downregulation of its cellular receptors have in no way been excluded as mechanisms for improvement in our series. However, the fact that this mechanism was linked to improvement in nonangioedema populations does not prove that it is operative in our series. It is intriguing that the patients of Spector and Tan,¹ like ours, had rapid improvement within weeks of initiating omalizumab. This might improve the chances of identifying the mechanisms involved.

Regarding their query that lisinopril (in 1 case) may have been a confounder, it was discontinued more than 1 year before instituting omalizumab.

Angioedema and urticaria may occur independently or in combination. Nevertheless, idiopathic angioedema and urticaria,

although unique entities, are not specific diseases, and thus reflect heterogeneous underlying conditions, likely with distinct mechanisms. Therefore, it is possible that some cases of idiopathic angioedema may be truly allergic and mediated by IgE mechanisms, despite the fact that our current clinical and laboratory diagnostic tools cannot detect this. Conversely, some idiopathic urticaria patients may have non-IgE-mediated mechanisms. Omalizumab responsiveness suggests a mechanistic overlap between these 2 conditions. We hope that our case series will stimulate both discussion of and investigation into mechanisms of angioedema and the apparent therapeutic efficacy of omalizumab.

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Delayed allergic reactions to omalizumab: Are patients reporting all cases?

To the Editor:

We read with interest the article entitled "Delayed onset and protracted progression of anaphylaxis after omalizumab administration in patients with asthma" by Limb et al.¹ We write to describe a case of anaphylaxis to first administration of omalizumab that highlights the possibility of underreporting of reactions to this medication.

We treated a 44-year-old woman with severe persistent asthma with omalizumab. Asthma was diagnosed at 28 years of age and had remained poorly controlled in spite of optimal inhaled and oral therapies, including oral corticosteroids. Her serum IgE level was 190 kU/L, with a positive RAST result to house dust mite. *Aspergillus* species antibodies were negative, and her peripheral eosinophil count was $0.8 \times 10^9/L$ (range, $0.0-0.4 \times 10^9/L$). She was initiated on omalizumab therapy and observed in the hospital for 2 hours after administration, when she was reviewed by an attending respiratory physician and was well.

Two and a half hours after administration of omalizumab, while driving in her car, the patient experienced throat irritation, pruritus of her ears, and wheeze requiring use of inhaled salbutamol. Four hours after administration, she noticed lip and tongue swelling and periorbital edema. Reluctant to report her symptoms to the hospital in the knowledge that omalizumab therapy would be terminated, she contacted her family practitioner, who prescribed desloratadine. However, she did ask her family to take a digital photograph of her 5 hours after treatment (Fig 1). Her facial symptoms persisted until the following day, when she self-medicated with high-dose oral corticosteroids, resulting in symptom resolution over the following 24 hours. When the patient reconsidered and reported the reaction 3 days later, we asked her to take comparison photographs in the same clothing with the same background (Fig 1). The patient consented to medical publication of her images without blacking of her eyes, given the serious implications of this reaction for practitioners and patients.

This patient's presentation was typical of the series of patients reported by Limb et al.¹ In this group the mean age was 43 years, with a majority of female subjects, many of whom had delayed onset and protracted progression of symptoms. Our patient,



FIG 1. Patient 5 hours after first dose of omalizumab (left) and 3 days afterwards following treatment (right).