

A Better IgE Trap to Control Urticaria

David M. Center, M.D.

Chronic spontaneous urticaria is a benign disease with symptoms that adversely affect quality of life, such as disrupted sleep, distracting pruritus, and unsightly wheals.¹ Spontaneous attacks without identifiable triggers render prevention impossible. As a result, the therapeutic goal is complete remission.² Remission is important because it also eliminates the itch–scratch–dermatographism–itch feedback loop that can result in cutaneous scarring. Most patients have a response to escalating doses of nonsedating antihistamines at four times the recommended daily dose. For persistent hives, second-line therapy is omalizumab²; this means that treatment costs escalate, from generic antihistamines that cost \$10 per month to a biologic agent that costs 200 times as much. For the patients who are made miserable by chronic spontaneous urticaria, and because omalizumab can result in complete remission in 35 to 53% of patients and partial remission in up to 70% of patients^{3–6} with few side effects, it is worth the cost. Unfortunately, many patients have resistance to remission with omalizumab therapy. We need better therapeutic agents because all the other effective drugs¹ have contraindications for use and serious potential side effects.

In this issue of the *Journal*, Mauer et al.⁷ report the results of a small, international trial assessing the safety and efficacy of omalizumab, at a dose of 300 mg per month, as compared with three doses of ligelizumab. Both antibodies bind IgE and presumably act by removing IgE from Fc epsilon receptor signaling complexes on the mast-cell surface. In an earlier study, ligelizumab was found to suppress the results of skin-prick tests to a greater extent and duration than omalizumab,⁸ thus providing equipoise for the trial published in the *Journal*. The primary end point of the trial conducted by Mauer et al. was complete control of hives, defined as a weekly hives-severity score of 0 (on a scale from 0 to 21). Absence of hives, along with complete control of itching, is the clinical therapeutic goal for all patients. More patients receiving the 72-mg or 240-mg dose of ligelizumab each month had

remission at 12 weeks than those receiving omalizumab.

The trial is interesting for several reasons. First, although the number of patients who did not have a response to omalizumab was higher in this trial than in other studies,^{3–5} since this is a head-to-head trial, it is reasonable to infer that the comparison between ligelizumab and omalizumab is valid. Second, the authors included a group of patients who received a single 120-mg dose of ligelizumab to test duration of effect. The percentage of patients in the single-dose group who had a complete response was similar to that observed with the 72-mg and 240-mg doses, but more importantly, the effect lasted 8 weeks, which suggests that standard administration of ligelizumab may be less frequent than that with omalizumab. Mauer et al. report no episodes of anaphylaxis with either monoclonal antibody. This observation is important because we need markers to identify the risk of anaphylaxis in order to permit the self-administration of biologic therapy by patients. Last, unfortunately, more than 50% of the patients with resistance to antihistamine therapy also had resistance to ligelizumab.

Although ligelizumab appears to be a better IgE trap than omalizumab, many questions remain. Do patients who do not have a response to double therapy (i.e., antihistamines aimed at end-organ inhibition and IgE trapping) that inhibits mast-cell signaling have a disease that is caused by different mechanisms than the disease in patients who do have a response? Will patients with angioedema and wheals have a better response to different therapies for symptom control than patients without these features of chronic spontaneous urticaria? That is, do these symptoms represent different causes? Unfortunately, current biomarkers for prognosis and drug responsiveness⁹ are nonspecific and do not identify treatment-responsive phenotypes. Because of the large percentage of patients who do not have a response to antibodies to IgE, we still need drugs with low toxicity, preferably those that act by means of alternative mecha-

nisms. At present, there are no mast-cell-stabilizing agents that can be delivered to skin mast cells to treat patients with chronic spontaneous urticaria, but there is promise in dupilumab, which lowers IgE levels by inhibiting interleukin-4 signaling. Dupilumab has been reported to suppress hives, has an excellent safety profile, and can be administered by patients themselves.¹⁰ Dupilumab is currently being investigated in a clinical trial involving patients with chronic spontaneous urticaria (ClinicalTrials.gov number, NCT03749135).

In summary, ligelizumab therapy appeared to control hives in a higher percentage of patients than omalizumab therapy, and the effects of a single 120-mg dose of ligelizumab lasted as long as 8 weeks. Are we ready to adopt ligelizumab as the initial second-line therapy after such a small trial? Should we switch to using ligelizumab in patients with omalizumab-resistant disease before adding more toxic drugs such as cyclosporine? Will ligelizumab be effective in patients with atopic dermatitis, asthma, or allergic rhinitis? These questions await greater clinical experience with the drug and larger trials. However, an anti-IgE therapy that induces remission in more patients with a longer interval between administration of the drug is much appreciated and should gain clinical popularity. We all await better understanding about the causes of chronic spontaneous urticaria as we search for good predictive markers for responses to therapy.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

From the Boston University Clinical and Translational Science Institute, Boston Medical Center, and Boston University — both in Boston.

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