Ligelizumab for Chronic Spontaneous Urticaria

TO THE EDITOR: Maurer et al. (Oct. 3 issue)[1] report on a phase 2b dose-finding trial examining the efficacy of ligelizumab in the treatment of chronic spontaneous urticaria. They found that ligelizumab outperformed omalizumab, and the maximum effect was observed at a dose of 72 mg. The authors controlled for the Chronic Urticaria Index (CU Index) score in analyses of secondary end points. However, they did not stratify the effect according to a positive CU Index or the degree to which the IgE level was elevated at baseline.

Although it would be a post hoc analysis, it would be interesting to know whether these biomarkers, which are currently largely used for prognostication,[2,3] had the potential for use in therapeutic planning. It is possible that the effectiveness of a given dose of ligelizumab differs according to the degree to which the IgE level is elevated or according to CU Index status.

Jeffrey M. Cohen, M.D.

Yale School of Medicine
New Haven, CT
jeffrey.m.cohen@yale.edu

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TO THE EDITOR: Maurer et al. report on a controlled comparison of ligelizumab with omalizumab in patients with chronic spontaneous urticaria. In an editorial in the same issue, Center[1] suggests that ligelizumab is a better anti-IgE therapy than omalizumab. However, both agents were associated with an absence of urticaria in less than half the patients in this trial.

In contrast, in two other trials, a complete resolution of urticaria occurred a median of 7 days after initiation of cyclosporine in all 23 adolescents who received this agent for antihistamine-resistant chronic spontaneous urticaria.[2,3] No adverse effects were reported in any of the patients. Unlike previous studies of cyclosporine for chronic spontaneous urticaria, the reliably absorbed microemulsion formulation of cyclosporine was used with therapeutic drug monitoring.[4] After a very slow taper of cyclosporine, remission continued in most patients after discontinuation of the drug. Only 5 patients had a recurrence a median of 6 months after discontinuation, with a prompt response once they began to receive cyclosporine again.

For chronic spontaneous urticaria that is resistant to high-dose antihistamines, our experience suggests that cyclosporine is a safe, more effective, less expensive regimen than currently available anti-IgE medications. More controlled clinical trials of the microemulsion formulation with therapeutic drug monitoring are warranted.

Miles Weinberger, M.D.

University of California, San Diego
San Diego, CA
miles-weinberger@uiowa.edu

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THE AUTHORS REPLY: We agree with Cohen that the effects of serum autoreactivity and IgE levels on the outcome of ligelizumab treatment in patients with chronic spontaneous urticaria warrant further study. A post hoc analysis of whether CU Index status or the degree to which the IgE level is elevated at baseline affects the response to ligelizumab could be of interest. It has previously been suggested that the CU Index could help in determining whether treatment more aggressive than an antihistamine is needed in patients with chronic spontaneous urticaria. Furthermore, in one trial,[1] among patients who had

chronic spontaneous urticaria and a positive CU Index (an indicator of a type IIb autoimmune cause), those who received omalizumab had a slower response and a lower response rate than those who did not. In our article, we noted that the rate of complete response was lower among patients who received omalizumab than the rate reported in previous studies, and this could be related to the higher percentage of patients with a positive CU Index at baseline. High baseline IgE levels have been shown to predict a faster response to omalizumab, as well as a faster return of symptoms after relapse.

We respectfully disagree with Weinberger's suggestion that cyclosporine is more effective than omalizumab or ligelizumab in the treatment of patients with chronic spontaneous urticaria. First, head-to-head trials are lacking to conclusively compare the outcomes of treatment with cyclosporine, omalizumab, and ligelizumab in patients with this condition. Second, Weinberger cites two studies of cyclosporine involving patients with chronic spontaneous urticaria, and these studies are small and uncontrolled. The highest reported rate of a complete response among patients with chronic spontaneous urticaria who received cyclosporine in a placebo-controlled trial was 26%, as compared with 70% among those who received omalizumab.[2] We also disagree with the notion that cyclosporine is a safe treatment option for patients with chronic spontaneous urticaria. A recent meta-analysis and systematic review showed that adverse events occurred in more than half the patients with this condition who received cyclosporine.[3] Our thinking follows the international guideline recommendations regarding the treatment of patients with chronic spontaneous urticaria from the European Academy of Allergology and Clinical Immunology, the Global Allergy and Asthma European Network, the European Dermatology Forum, and the World Allergy Organization, and we use cyclosporine only when antihistamines and omalizumab fail.[4]

Marcus Maurer, M.D.

Charité–Universitätsmedizin Berlin
Berlin, Germany
marcus.maurer@charite.de

Ana M. Giménez-Arnau, M.D., Ph.D.

Universitat Autònoma Barcelona
Barcelona, Spain

Martin Metz, M.D.

Charité–Universitätsmedizin Berlin
Berlin, Germany

Since publication of their article, the authors report no further potential conflict of interest.

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THE EDITORIALIST REPLIES: Weinberger raises the key issue in second-line therapy for hives: What is the best choice? In his experience with pediatric patients, cyclosporine is safe and effective and is much less expensive than biologic agents. I agree and noted that it is a very effective treatment in adult patients also. Unfortunately, many adult patients are women of childbearing age who — despite reassurance — balk at the use of cyclosporine when they read the long and troubling list of possible severe side effects. Although it is much more inconvenient and expensive than cyclosporine, anti-IgE therapy does not invoke fears of off-target organ damage and is readily accepted by patients. Oral second-line therapies with side-effect profiles that are better than those of cyclosporine in adult patients and good biomarkers to predict responsiveness to treatments are needed.

David M. Center, M.D.

Boston University Medical Campus
Boston, MA
dcenter@bu.edu

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