Editorial

Barzolvolimab: Targeting the effector cell in chronic spontaneous urticaria

Matthew P. Giannetti, MD[a,b] *Boston, Mass*

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Chronic spontaneous urticaria (CSU) is a mast cell–driven disease characterized by recurrent cutaneous wheals (urticaria), angioedema, or both. CSU affects up to 1% of the global population and is associated with a significant decrease in quality of life, disrupted sleep, depression, and anxiety. CSU is caused primarily by mast cell activation and subsequent release of proinflammatory mediators (notably, histamine) that drive peripheral vasodilation, capillary leak, and activate sensory nerves, leading to the hallmark symptoms of wheal, flare, and cutaneous pruritus.

The pathogenesis of CSU is not completely understood. Historically, 2 major pathways leading to mast cell activation have been described: type I CSU (autoallergy), which involves IgE directed at the self, and type IIb CSU, which is driven by IgG autoantibodies against FcεRI and/or IgE.[1] More recent data indicate considerable overlap between these 2 mechanisms.[2] More importantly, 16% of patients do not have autoantibody markers characteristic of either disease type.[2] Regardless of mechanism, the result is direct mast cell activation resulting in mediator release, as depicted in Fig 1.

There is a major unmet need for additional therapeutic options in CSU. Since 2014, omalizumab has been the sole biologic for treatment of CSU; however, approximately half of patients treated with the US Food and Drug Administration–approved dose of omalizumab have failed to respond.[3,4] This led to the development of Bruton tyrosine kinase inhibitors for CSU, which target the signaling pathway downstream of FcεRI. Recent phase 3 clinical trials (REMIX-1 and REMIX-2) demonstrated that remibrutinib provides symptom control (Urticaria Activity Score summed over 7 days [UAS7] < 6) at week 12 in approximately half of enrolled participants. Clearly, despite therapeutic advances, a subset of patients remain refractory to these therapies and/or fail to achieve complete symptom resolution. These patients are often prescribed immunosuppression, which subjects patients to an unacceptable level of toxicity.

Barzolvolimab represents a promising therapeutic option, as it is the first therapy to directly deplete the end-effector cell in patients with CSU.[5] In this issue of the *Journal of Allergy and Clinical Immunology*, Metz et al present data from a phase 2 dose-finding study of the mAB barzolvolimab.[6] Barzolvolimab is a humanized IgG_1 antibody directed at the extracellular domain of the KIT receptor. The binding of barzolvolimab occupies much of the KIT receptor and sterically hinders stem cell factor access to KIT, as depicted in Fig 1. As KIT signaling is an essential component of mast cell maturation and survival, blockade of this pathway depletes tissue-resident mast cells.

The study included 208 adults with moderate-to-severe CSU (defined as UAS7 > 16) despite treatment with oral H1-antihistamines at up to 4 times the approved dose. Subjects were randomized 1:1:1:1 to receive barzolvolimab at a dose of 75 mg every 4 weeks, 150 mg every 4 weeks, 300 mg every 8 weeks, or placebo. Barzolvolimab showed statistically significant improvements for all end points, including UAS7 (including the component scores Itch Severity Score summed over 7 days and Hives Severity Score summed over 7 days) and AAS Angioedema Activity Score over 7 days. Symptoms improved quickly, with significant improvements noted after 2 weeks of therapy. By week 12, 41.7% to 62.5% of patients had well-controlled disease (UAS < 6) depending on the dose of the study drug.

Although barzolvolimab was well tolerated, its mechanism of action raises concern for "on-target" side effects, given that the receptor tyrosine kinase KIT is widely expressed. First, KIT is expressed at high levels in melanocytes, and 9% of barzolvolimab-treated patients had hair hypopigmentation (although this figure was higher in the phase 1b study).[5] Second, KIT is necessary for spermatogenesis and gustatory senses; inhibition leads to reversible spermatogenesis defects and dysgeusia, respectively.[7-9] Finally, KIT is expressed in multiple hematopoietic lineages, which led to neutropenia in 7.7% of patients. Despite the neutropenia, infections were not increased in the subjects with neutropenia or in those study participants in general. Given the likelihood of prolonged exposure in a chronic disease such as CSU, barzolvolimab's safety profile warrants monitoring in phase 3 trials.

Barzolvolimab is the first mAb capable of depleting tissue-resident mast cells. In the present study, tissue mast cell depletion is implied via significant reduction in baseline serum tryptase level. More compelling evidence was demonstrated in an early phase 1b study of barzolvolimab in patients with chronic inducible urticaria; in that study, Terhorst-Molawi et al showed a statistically significant reduction in human skin mast cells, as assessed by anti-tryptase and anti-CD117 immunohistochemical staining as early as 1 week after exposure to barzolvolimab.[10] Direct tissue depletion of mast cells has been shown only in the skin, and further studies are needed to prove similar effects in the gastrointestinal tract, lung, and other organs. On the basis of this mechanism of action, similar results would be expected for other organs.

The capacity to deplete tissue-resident mast cells has profound treatment effects on other disorders driven by mast cell activation. Mast cell activation disorders are a collection of disorders broadly classified as clonal or nonclonal. The landscape of therapy in

From [a]the Division of Allergy and Clinical Immunology, Brigham and Women's Hospital, Boston, and [b]Harvard Medical School, Boston.

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Corresponding author: Matthew Giannetti, MD, Division of Allergy and Clinical Immunology, Brigham and Women's Hospital, 60 Fenwood Rd, Hale Building for Transformational Medicine, 5th Floor, Boston, MA 02132. E-mail: mgiannetti@bwh.harvard.edu.

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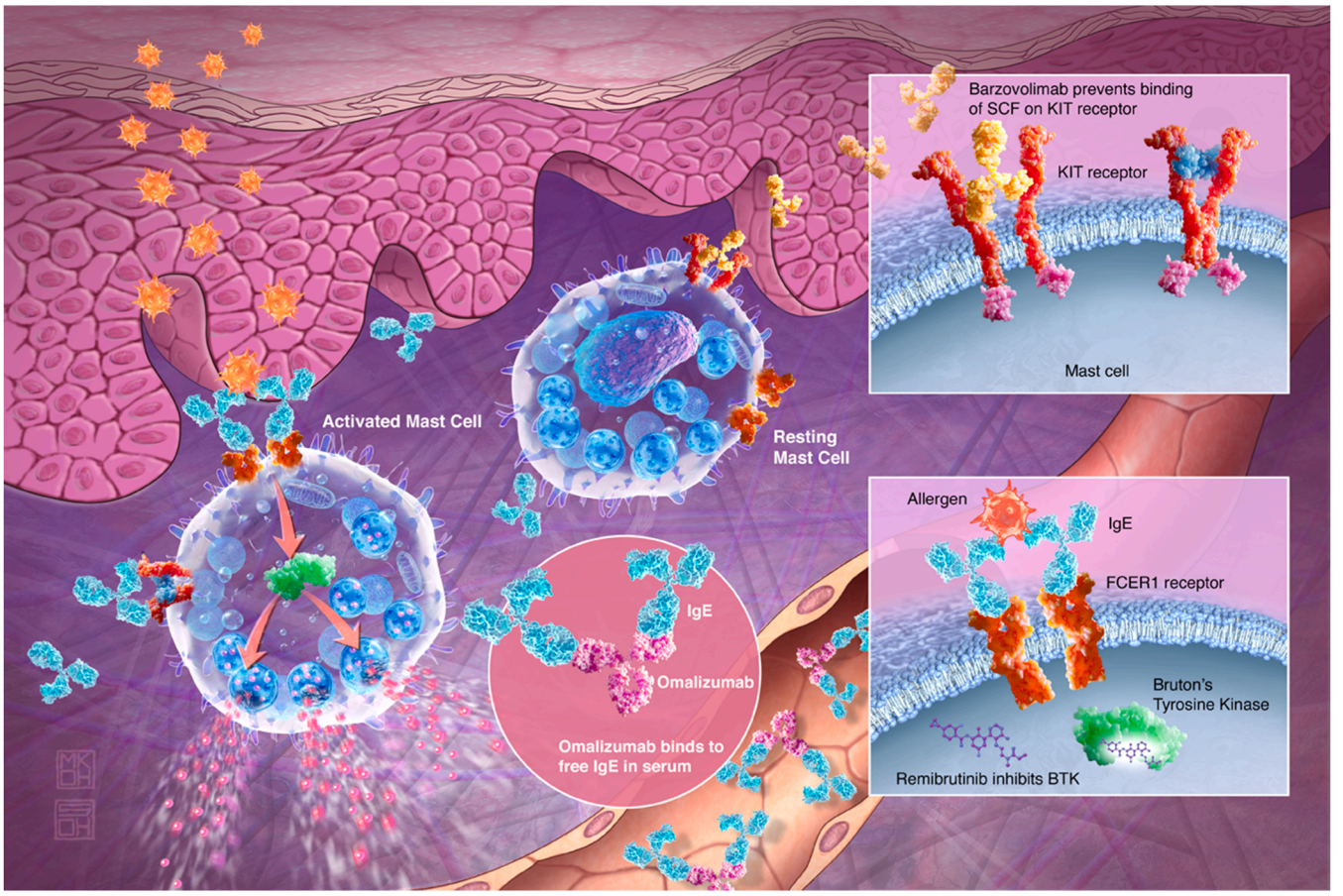

FIG 1. Barzolvolimab's mechanism of action. Barzolvolimab binds the extracellular domain of KIT and inhibits stem cell factor (SCF) binding. Omalizumab directly binds IgE and prevents interaction with the IgE receptor (FcεRI). Remibrutinib binds Bruton tyrosine kinase (BTK) within the mast cell.

clonal disorders has changed dramatically in the past several years with the advent of avapritinib, bezuclastinib, and several ongoing clinical trials. These medications are targeted at the primary driver mutation in clonal mast cell disease, namely, KIT D816V. In contrast, the nonclonal disorders do not have a defining mutation and are poorly understood mechanistically. There is a lack of therapeutic options for this patient population.

The nonclonal mast cell activation disorders are fundamentally characterized by mast cell activation. As a result, therapies targeting mast cells and mast cell pathways have been co-opted from other indications. Omalizumab has frequently been utilized, but this medication is generally limited to mast cell activation within the IgE pathway. Direct cytoreduction of tissue-resident mast cells with available therapies has not been possible. In theory, the ability to deplete tissue-resident mast cells would be a definitive therapy for the nonclonal mast cell activation disorders. Outside the mast cell activation disorders, there are many other mast cell–driven conditions for which barzolvolimab may have therapeutic benefit. This would include asthma, food allergy, and possibly allergic rhinoconjunctivitis. A better understanding of the efficacy and safety profile will be necessary to assess the risks and benefits in other disorders.

In summary, barzolvolimab is a promising new therapy with a novel mechanism of action targeting the KIT receptor. Barzolvolimab has potential to address the substantial unmet needs of patients with CSU. The early phase 2 results presented by Metz et al[6] provide a strong foundation for the definitive phase 3 trial, EMBARQ-CSU, which is currently ongoing.

Human and animal rights and informed consent. This article does not contain any studies with human or animal subjects performed by any of the authors.

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