The potential pharmacologic mechanisms of omalizumab in patients with chronic spontaneous urticaria

Tse Wen Chang, PhD,[a] Christina Chen, BS,[a] Chien-Jen Lin, PhD,[a] Martin Metz, MD,[b] Martin K. Church, PhD, DSc,[b] and Marcus Maurer, MD[b] *Taipei, Taiwan, and Berlin, Germany*

In patients given a diagnosis of chronic spontaneous urticaria (CSU), there are no obvious external triggers, and the factors that initiate the clinical symptoms of wheal, flare, and itch arise from within the patient. Most patients with CSU have an autoimmune cause: some patients produce IgE autoantibodies against autoantigens, such as thyroperoxidase or double-stranded DNA, whereas other patients make IgG autoantibodies against FcεRI, IgE, or both, which might chronically activate mast cells and basophils. In the remainder of patients with CSU, the nature of the abnormalities has not yet been identified. Accumulating evidence has shown that IgE, by binding to FcεRI on mast cells without FcεRI cross-linking, can promote the proliferation and survival of mast cells and thus maintain and expand the pool of mast cells. IgE and FcεRI engagement can also decrease the release threshold of mast cells and increase their sensitivity to various stimuli through either FcεRI or other receptors for the degranulation process. Furthermore, IgE-FcεRI engagement potentiates the ability of mast cells to store and synthesize *de novo* inflammatory mediators and cytokines. Administration of omalizumab, by virtue of its ability to deplete IgE, attenuates the multiple effects of IgE to maintain and enhance mast cell activities and hence reduces the ability of mast cells to manifest inflammatory mechanisms in patients with CSU. (J Allergy Clin Immunol 2015;135:337-42.)

Key words: *Chronic urticaria, omalizumab, IgE, FcεRI, autoantibodies, mast cells, activation/release threshold, IgE–FcεRI–mast cell axis*

Abbreviations used
ASST: Autologous serum skin test
CSU: Chronic spontaneous urticaria
CU: Chronic urticaria
dsDNA: Double-stranded DNA
HC: Highly cytokinergic
ssDNA: Single-stranded DNA
TPO: Thyroperoxidase

Chronic spontaneous (idiopathic) urticaria (CSU) is characterized by the presentation of itchy wheal-and-flare skin reactions, angioedema, or both for a period of greater than 6 weeks.[1] For most patients with severe CSU, damage to their appearance and the unbearable itching extend beyond a physical ailment to psychological disorders, including anxiety and depression, and severely impair the patient's quality of life.[2] Although the symptoms of the majority of patients can be adequately treated with antihistamines, in many cases they cannot. In these cases it is necessary to consider second-line treatments.[3]

Between 2006 and 2008, a number of physician-initiated case reports and pilot studies on CSU,[4] chronic autoimmune urticaria,[5] idiopathic angioedema,[6] cold-induced urticaria,[7] cholinergic urticaria,[8] and solar urticaria[9] showed that the humanized anti-IgE antibody omalizumab was efficacious against urticarial diseases not adequately treated with other medications. These reports spurred subsequent broader investigation of the effects of omalizumab in patients with chronic urticaria (CU).

To date, 2 phase II[10,11] and 4 phase III multicenter, randomized, placebo-controlled clinical trials[12,13] have convincingly established that omalizumab is efficacious and safe for treating recalcitrant CSU that cannot be adequately treated with current standard care. Furthermore, a retrospective clinical analysis of 51 patients in Germany has shown omalizumab to be a rapidly acting, highly effective, and safe drug in both patients with CSU and those with chronic inducible urticaria.[14] A summary of the clinical studies of omalizumab in patients with urticaria is shown in Table E1 in this article's Online Repository at www.jacionline.org.

Omalizumab, which has been conceptualized for treating IgE-mediated allergic diseases[15] and approved for treating patients with severe persistent allergic asthma in many countries, can neutralize IgE, impede the IgE allergic pathway, and render mast cells and basophils insensitive to activation through IgE/FcεRI.[16,17] Although reports showing the therapeutic effects of omalizumab on CSU have suggested a mechanism by which it attenuates the pathology of CSU with an autoimmune cause, such analyses are largely simplistic and incomplete. Furthermore, there is a nearly complete void of explanation in the literature on how omalizumab might achieve its therapeutic effects in patients with CSU and chronic inducible urticaria. This review will focus on CSU and the possible mechanism or mechanisms by which omalizumab might be effective in its treatment.

HISTAMINE, MAST CELLS, AND CSU

The activation of mast cells and their release of inflammatory mediators are regarded as the "final common pathway" for a myriad of proinflammatory factors, including those involved in

From [a]the Genomics Research Center, Academia Sinica, Taipei, and [b]the Department of Dermatology and Allergy, Charité-Universitätsmedizin Berlin.

Disclosure of potential conflict of interest: T. W. Chang has received research support grant no. NSC-2320-B-001-005 from Nation Science Council Taiwan. M. Metz has consultant arrangements with and has received research support and honoraria for lectures from Novartis, Switzerland. M. K. Church has received payment for lectures from Novartis, Switzerland. M. Maurer has received honoraria for lectures and consulting, and funding for research from Novartis, Switzerland and Genentech. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication February 24, 2014; revised April 26, 2014; accepted for publication April 30, 2014.

Available online June 17, 2014.

Corresponding author: Martin K. Church, PhD, DSc, Allergie-Centrum-Charité, Department of Dermatology and Allergy, Charité-Universitätsmedizin Berlin, Charitéplatz 1, D-10117 Berlin, Germany. E-mail: mkc@soton.ac.uk.

0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2014.04.036

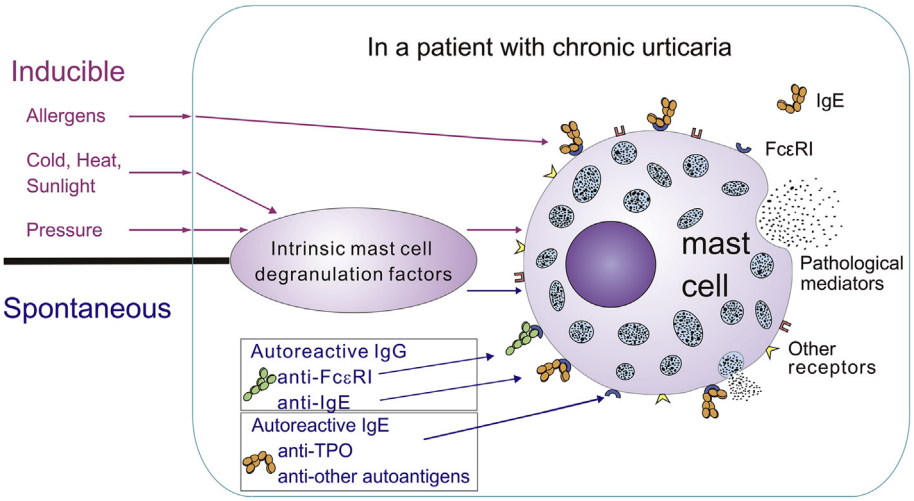

FIG 1. The inflammatory manifestation of mast cells in affected skin is the final common pathway in various types of urticaria. For the inducible subtypes, there are identifiable external triggers. For physical urticaria, the internal pathologic factors that transduce external triggers to mast cell activation have not been identified. For the spontaneous type, the primary causative factors that cause the urticarial manifestation arise internally. In one large subtype the patients have an autoimmune cause. For the remaining cases of the spontaneous type, the internal abnormalities have not been identified.

the various types of urticaria,[18,19] as shown in Fig 1. The clinical response of CSU to H_1-antihistamines and the finding of increased concentrations of histamine in skin tissue fluid underscore the role of histamine derived from dermal mast cells as a major mediator of urticaria.[20] But what stimulates mast cells to degranulate, and why does this happen in the skin?

Although highly unlikely, it cannot be excluded that in some cases of CSU, the primary abnormality lies in the mast cells themselves (eg, because of intrinsic or genetic alterations that cause altered activities of signal transduction pathways, as occurs in mastocytosis).[21] If this were the case, it would be likely that the condition would be systemic rather than confined to the skin. Therefore it is more likely that skin mast cells in patients with CSU are not intrinsically abnormal but become increasingly sensitive or "unstable" or activated as the result of certain abnormal factors present in their surroundings.

Although there are many nonimmunologic factors that might influence mast cell function in the skin, such as components of the complement system[22] and neuropeptides, particularly those related to stress,[23] because this review is primarily concerned with the mechanisms by which omalizumab might be effective, nonimmunologic factors will not be considered in detail.

A STATE OF MAST CELL ACTIVATION WITHOUT DEGRANULATION: PRIMING MAST CELLS FOR FULL ACTIVATION

Accumulating evidence in the literature suggests that the IgE–FcεRI–mast cell axis does not merely exist in idled and triggered states. Before mast cells become productively activated for mediator release, they exist at some point along a spectrum of activation states of increasing potency. In other words, the activation of mast cells does not necessarily lead to their degranulation but might serve to prime them for subsequent activation. We will consider 2 possible mast cell–priming pathways for urticaria, namely the heterogeneous effects of monomeric IgE and the consideration of CSU as an autoreactive disease (Fig 2).

MONOMERIC IgE POTENTIATES THE ACTIVITIES OF MAST CELLS IN THE ABSENCE OF ALLERGEN CROSS-LINKING

In conventional thinking the involvement of IgE in mast cell activation requires the cross-linking of FcεRI-bound IgE by antigen or anti-IgE antibodies. This initiates the aggregation of FcεRI, leading to tyrosine kinase activation and subsequent mast cell activation for secretion. However, in 2001, it was suggested independently by 2 groups[24,25] that monomeric IgE in the absence of antigen can have multiple effects in murine mast cells, including differentiation, proliferation, survival, and mediator and cytokine generation. These effects, which involve the binding of IgE to FcεRI and the aggregation of FcεRI, occur without the mast cells undergoing degranulation.[24]

The finding that monomeric IgE can augment mast cell activity has been confirmed by studies using various techniques. In a transcriptome analysis of 8793 genes, sensitization of mast cells with monoclonal IgE alone, without FcεRI cross-linking, was found to upregulate 58 genes more than 2-fold compared with their levels in unsensitized mast cells.[26] These genes included those for cytokines, such as IL-1β, IL-6, and colony-stimulating factor 1; chemokines, such as IL-8 (CXCL8), CCL4, and monocyte chemoattractant protein 1 (CCL7); and cytokine and chemokine receptors. The genes for various immune regulators, adhesion molecules, antiapoptosis proteins, and cytoskeletal elements, such as RAS protein activator like 1 (*RASAL1*) and fibronectin leucine-rich transmembrane protein 2 (*FLRT2*), were also upregulated.

Other studies have followed the suggestion that mouse monoclonal IgE molecules are heterogeneous with respect to their ability to induce survival and activation events in mast cells.[27] At one end of the spectrum, highly cytokinergic (HC)