Biologics in Chronic Urticaria

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KEYWORDS

• Chronic urticaria • Biologics • Omalizumab • Therapy • Rituximab • TNF antagonist • Intravenous immunoglobulin therapy

KEY POINTS

- Omalizumab is the only monoclonal antibody that is approved for chronic urticaria (CU).
- Randomized, placebo-controlled trials and extensive clinical experience show that omalizumab is both safe and efficacious for CU.
- A few reports demonstrated effectiveness of high-dose immunoglobulin therapy.
- Weak evidence supports rituximab and tumor necrosis factor antagonist efficacy in antihistamine-refractory CU.

Chronic urticaria (CU), also referred to as chronic spontaneous urticaria, is defined as wheals, angioedema, or both lasting longer than 6 weeks.[1] CU is associated with intense pruritus, disfiguring wheals, and higher odds of reporting depression, anxiety, and sleep difficulty.[2–4] Patients with CU experience a tremendous burden, with quality-of-life estimates on par with patients with coronary artery disease awaiting bypass.[5,6] Urticaria of any type is estimated to have a lifetime prevalence of 8.8%, whereas CU has an annual prevalence of 0.5% to 5.0% and a lifetime prevalence rate of 1.8%.[2,7–12] The first-line therapies for CU are second-generation H_1 antihistamines, often required at 2 to 4 times the doses approved by the Food and Drug Administration (FDA).[12] Unfortunately, many patients will fail antihistamines and will require alternative therapies to control their symptoms. For these patients, biologics have proven to be relatively safe and efficacious.

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The FDA defines biologics as a wide range of products, such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins.[13] Although biologics have been used for years, the first licensed monoclonal antibody (mAb) was muromonob-CD3, an mAb directed at CD3, in 1986.[14] Since then, the use of targeted biological therapies has expanded. For the treatment of the urticarial diseases, mAb, recombinant antagonists, and donor immunoglobulin have played important roles (**Fig. 1**). The most important biologic used in CU is omalizumab.

ANTI–IMMUNOGLOBULIN E MONOCLONAL ANTIBODIES

Overview and Mechanism of Action of Omalizumab

Although the exact cause of CU is not entirely known, many patients have autoantibodies to the alpha chain of the high-affinity receptor FcεR1 or to immunoglobulin (Ig)E, with the former more specific for CU.[15] Omalizumab is a recombinant humanized monoclonal anti-IgE antibody that binds to the C epsilon 3 domain of IgE (the site of high-affinity IgE receptor binding) and inhibits it from binding to the cell receptor.[16,17] Omalizumab binds to the free IgE, leading to a reduction of free IgE levels and, consequently, decreased expression of FcεRI receptors on mast cells, basophils, and dendritic cells.[18–22] This effect may reduce mast cell numbers, as mast cell proliferation and survival are theorized to depend on IgE-FcεRI–dependent pathways.[23] It is also

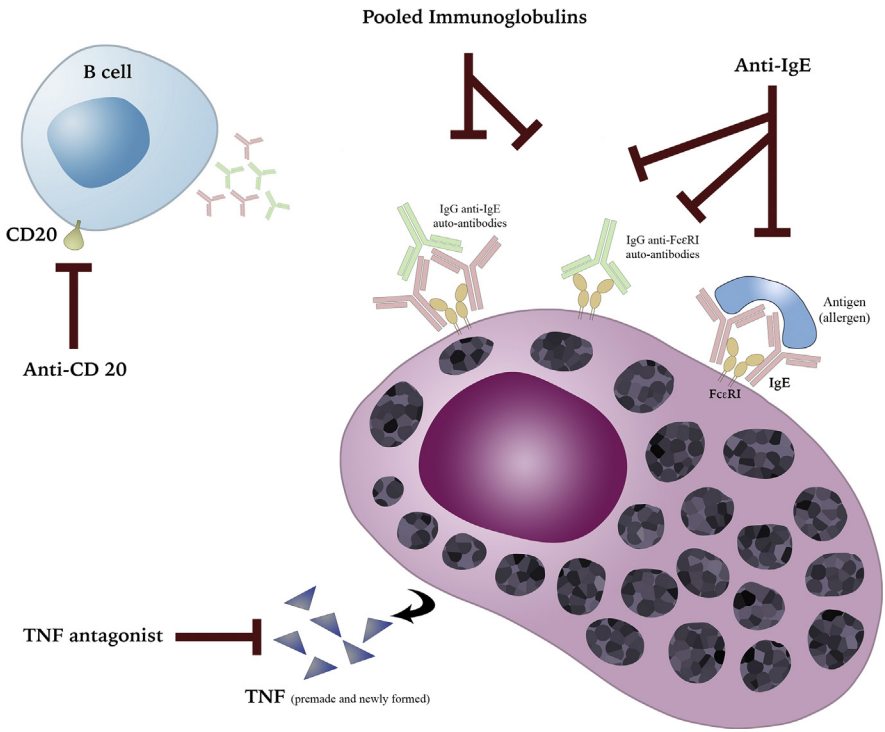

Fig. 1. The proposed mechanism of action of different biological agents in CU. Anti-IgE blocks the effect of IgE at the level of IgE-antigen cross-linking, IgE–anti-IgE IgG cross-linking, and anti-FcεRI IgG (downregulation). Anti-CD20 blocks CD20 B cells. TNF antagonist blocks both premade and newly synthesized TNF.