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Perspective

Treatment with omalizumab or cyclosporine for resistant chronic spontaneous urticaria

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Introduction

Chronic spontaneous urticaria (CSU) is classified as urticaria with or without angioedema that occurs for 6 or more weeks with an unknown cause. The prevalence of CSU (also known as chronic idiopathic urticaria) is approximately 0.5% to 5% of the population. CSU may be active or reactivated for 1 to 5 years at a time, but in some cases, CSU can relapse, lasting several years.[1] CSU has deleterious effects on patients' quality of life, overall health, and emotional well-being.[2] Although guidelines outline several options for treating CSU, many patients ultimately resort to last-line therapies.[1] In this article, the 2 mainstay last-line treatment options for CSU, omalizumab and cyclosporine, are compared.

According to US guidelines, first-line treatment for CSU is the use of second-generation histamine$_1$ (H_1) antihistamines (ie, cetirizine). Although effective for some urticaria, second-generation H_1-antihistamines, even at doses up to 4 times the maximum approved dose, are often ineffective for CSU. The second step in therapy is the addition of another second-generation H_1-antihistamine, addition of an H_2-receptor antagonist, addition of a leukotriene receptor antagonist, or addition of a first-generation antihistamine (ie, diphenhydramine) taken at bedtime. If treatment with this approach also fails, a potent antihistamine (ie, hydroxyzine) can be dose advanced until no longer tolerated. This treatment is often ineffective and may have adverse effects, such as drowsiness, that affect patients' quality of life. The next step is last-line alternative treatments, including immunosuppressants, such as cyclosporine; biologics, such as omalizumab; or anti-inflammatories. Although omalizumab is approved by the US Food and Drug Administration for CSU, cyclosporine and the other last-line agents are not.[1] European guidelines, similar to US guidelines, recommend a second-generation H_1-antihistamine first line, increasing its dosage up to 4-fold second line, and adding omalizumab, cyclosporine, montelukast, or a short course of corticosteroids for exacerbations third line.[3] Data that support the last-line agents are limited, and some of these agents when taken long term have significant adverse effects. Because the mechanism of CSU is debatable, the-last line agents' mechanisms are theorized based on the hypothetical pathophysiologic mechanisms of the disease.

Histamine release from mast cells causes urticaria and in some cases angioedema. In CSU, there are several ways that histamine release from mast cells may be occurring via IgE and non–IgE-mediated pathways. A detailed description of the pathophysiologic mechanism of CSU is beyond the scope of this article and is comprehensively reviewed elsewhere.[2]

Select Treatments for Resistant CSU

Omalizumab, a monoclonal antibody against IgE, is the first biologic agent approved for CSU. It is administered subcutaneously at doses of 150 or 300 mg every 4 weeks (Table 1). The duration of treatment needed for CSU has not been determined, so patients should be monitored for resolution of urticaria. Monitoring IgE levels during treatment is not recommended because dosing and treatment duration of omalizumab for CSU are not based on IgE levels. IgE levels may increase during omalizumab treatment because of the presence of omalizumab-IgE complexes. Most commercial assays detect total and not free IgE. Patients should be monitored for adverse drug reactions, including anaphylaxis and injection site reactions, on administration.[4,5]

Cyclosporine, an immunosuppressant agent that inhibits T lymphocytes, is used off label for refractory CSU and has been studied at doses of 1 to 5 mg/kg daily. Cyclosporine is available in modified and unmodified versions. Unmodified cyclosporine has less absorption than the modified version and thus lowers bioavailability, making the 2 products not interchangeable. Before starting cyclosporine treatment, patients should have their blood pressure checked on 2 separate occasions, and baseline laboratory components, including blood urea nitrogen, serum creatinine, complete blood cell count, magnesium, lipids, potassium, and uric

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Table 1
Comparison of Omalizumab and Cyclosporine[2,4–7]

Variable	Omalizumab (Xolair)	Cyclosporine
Use	FDA approved for CSU	Off label for CSU
Proposed mechanisms for CSU	• IgG monoclonal antibody • Binds to IgE • Lowers free IgE levels • Downregulates FcεRI on cells	• Immunosuppressive agent • Known to reduce IgG, IgE, and FcεRI • Other proposed mechanisms — Immunoglobulin inhibition in activated B cells when T leukotrienes are present decreases the amount of IgG, IgE, and FcεRI — IL-2 inhibition via inhibition of T-cell–mediated autoimmune responses; inhibition of IL-2 indirectly inhibits mast cell degranulation — Effect on intracellular calcium concentration causes inhibition of mast cell degranulation to prevent release of histamine
Route	Subcutaneous injection given in practitioner's office	Oral
Frequency	Every 4 weeks	Once or twice daily
Monitoring	• Injection site reactions • Anaphylaxis upon administration	Baseline • Blood pressure, blood urea nitrogen, serum creatinine, lipids, potassium, magnesium Monthly during treatment • Blood pressure, redraw baseline laboratory samples Throughout Treatment • Adverse effects, signs and symptoms of infection
Pregnancy and lactation	Pregnancy • Limited human data • IgG molecules known to cross the placenta Lactation • Potential toxic effects • Excretion in breast milk is expected because of known excretion of IgG in breast milk	Pregnancy • Limited human data • Crosses the placenta • Adverse events were not observed in animal reproduction studies Lactation • Potential toxic effects • Excreted in breast milk
Cash Price/Month	1× 150-mg injection: $1,062 + fee for nurse visit	150 mg/d: $98 + monthly laboratory sample draw fees

Abbreviations: CSU, chronic spontaneous urticaria; FDA, US Food and Drug Administration; IL, interleukin.

acid, should be measured. Throughout treatment, initial laboratory samples should be redrawn monthly and during dosage adjustments. Patients should be monitored for adverse effects, including gum hyperplasia, hypertension, renal dysfunction, tremor, and hirsutism. Because cyclosporine is an immunomodulator, patients are at increased risk of infections and should be monitored for signs and symptoms of infection.[5,6]

Other treatment options suggested in the guidelines for refractory CSU have much less supporting evidence than omalizumab or cyclosporine. These options include hydroxychloroquine, dapsone, methotrexate, sulfasalazine, or intravenous immunoglobulin.[1]

Omalizumab Studies

Six major studies and 1 meta-analysis clinically analyzed omalizumab in patients with resistant CSU (Table 2).[8–14] All studies were multicenter, randomized, double-blind, and placebo-controlled. MYSTIQUE (Phase III Open Label First Line Therapy Study of MEDI 4736 [Durvalumab] With or Without Tremelimumab Versus SOC in Non Small-Cell Lung Cancer) was the only study not to include an antihistamine treatment in addition to omalizumab or placebo as part of its treatment protocol.[8] The studies enrolled 91 to 336 patients and had similar inclusion criteria involving age, duration and severity of CSU, and previous treatment. The duration of treatment ranged from 4 to 28 weeks. Different severity or quality-of-life measures were used as primary efficacy end points, including Urticaria Activity Score (UAS7), Itch Severity Scale (ISS), and the Chronic Urticaria Quality of Life Score (CU-Q2oL). Although each of these scales is slightly different, they all take into account itchiness and amount of hives.[8–14]

Omalizumab 75 mg, was effective vs placebo in 1 of its 3 studies. The 150-, 300-, and 600-mg doses were effective vs placebo in all studies in which they were used. According to the meta-analysis, 300 mg was the most effective dose. Adverse events were similar between omalizumab and placebo. Some adverse events that occurred with omalizumab were gastrointestinal upset and infusion site reactions.[8–14]

Cyclosporine Studies

Four studies assessed cyclosporine treatment in patients with resistant CSU (Table 3). All 4 studies used modified cyclosporine. Two studies were placebo-controlled,[15,16] 1 was open label,[17] and 1 was retrospective.[18] The doses of cyclosporine administered ranged from 1 to 5 mg/kg daily. The study enrollments ranged from 25 to 110 patients. The study durations ranged from 1 to 6 months. Different severity measurements were used as primary efficacy end points.[15–18] One study[17] also compared biomarkers thought to be involved in the pathophysiology of CSU.

All doses of cyclosporine studied were effective. Most adverse events that occurred were minor, such as gastrointestinal effects.[15–18] There were cases of mild increases in serum creatinine that required dose reductions.[18] In the study by Serhat et al,[17] significantly fewer biomarkers (interleukin 2 receptor, tumor necrosis factor α, and interleukin 5) were present in patients without CSU than with CSU. There was also a significant decrease in biomarkers in patients with CSU after taking cyclosporine.[16]

Conclusion

Both omalizumab and cyclosporine are effective treatment options for patients with resistant CSU. Omalizumab was most effective with 300 mg subcutaneously every 4 weeks. Cyclosporine was effective at doses ranging from 1 to 5 mg/kg daily. Overall, the