

Concomitant treatment with omalizumab and cyclosporine for chronic spontaneous urticaria



Chronic spontaneous urticaria (CSU) is defined as urticaria with or without angioedema occurring for more than 6 weeks without an identifiable etiology. Based on consensus guidelines, the first-line treatment consists of second-generation H₁ antihistamines of up to 4 times the maximum daily recommended dose.¹ However, 25% to 42% of patients may fail to achieve clinical response despite these regimens.^{2,3} Add-on therapies include first-generation H₁ antihistamines with or without a leukotriene receptor antagonist, whereas omalizumab or cyclosporine (CsA) are subsequent treatment considerations for CSU.¹

Omalizumab is the only United States Food and Drug Administration–approved next-line therapy for CSU based on scientific evidence reported in randomized, placebo-controlled trials.^{1,4–6} Alternatively, CsA may be prescribed off-label for CSU management in the United States.¹ Although typically used for organ transplant rejection prophylaxis, CsA can control CSU at comparatively lower doses. Omalizumab is regarded as the preferred add-on therapy because of its safety profile of having less toxicity, given that CsA may cause adverse effects such as renal dysfunction and hypertension.

Omalizumab-refractory CSU represents a difficult case for the patient and physician. Definitive management guidelines are lacking for these cases, and there are no formal studies investigating concomitant treatment with omalizumab and CsA. Herein, we report our institutional experience on patients with omalizumab-refractory CSU who received add-on therapy with very low-dose (<2 mg/kg/d) to low-dose (2–4 mg/kg/d) CsA.

We treated 6 adult patients (age range: 24–55 years; 4 women) with omalizumab-refractory CSU who started concomitant CsA. All patients had persistent urticaria with or without angioedema despite having received at least 12 weeks of omalizumab (300 mg every 4 weeks; median duration: 22 weeks [interquartile range: 15–29]). Four patients had elevated chronic urticaria indices. Two skin biopsies revealed mixed eosinophilic/neutrophilic infiltrates, whereas 1 was predominantly eosinophilic. Table 1 summarizes the patients' clinical characteristics.

Given the CSU severity, CsA was added, and omalizumab was continued in an attempt to lower the most effective CsA dose. All patients continued to receive omalizumab 300 mg every 4 weeks. Initial CsA doses ranged from 1.1 to 3.7 mg/kg/d (all started on 100 mg twice daily). During the treatment period, patients had follow-up visits with blood pressure and laboratory monitoring (complete blood cell count, renal/liver function, glycated hemoglobin, and random CsA levels) 2 to 4 weeks after CsA initiation, followed by every 1 to 3 months, unless dosing was increased. All patients achieved complete resolution (Urticaria Activity Score over 7 days [UAS7] = 0) while on both omalizumab and CsA (median time to resolution: 5 weeks [interquartile range: 1–15]). Maximum CsA doses ranged from 1.5 to 3.8 mg/kg/d, whereas the lowest maintenance doses ranged from 0.2 to 2.1 mg/kg/d. Three patients required up-titration (4–16 weeks after initiation) of CsA before achieving clinical resolution. If controlled, the CsA dose was lowered and the patient monitored for maintained clinical response. At most random monitoring points, subimmunosuppressive levels of CsA were detected; there were no toxic levels. Four patients successfully tapered off CsA, 1 patient continued to receive concomitant therapy and the other required intermittent CsA courses. Omalizumab continuation was

confirmed in 3 patients; 2 were lost to follow-up after CsA discontinuation. One patient was controlled with fexofenadine alone. One patient developed hypertension, which may have been related to CsA, although she had other underlying risk factors. Table 1 summarizes the CsA doses and administration and other treatment regimens.

Severe CSU unresponsive to omalizumab is especially challenging. Initial studies investigating omalizumab for CSU revealed that after 12 weeks of therapy (300 mg every 4 weeks), approximately 52% to 66% of patients achieved a partial response (UAS7 <6), whereas 34% to 44% achieved complete clinical response (UAS7 = 0).^{4–6} Likewise, Sánchez et al³ reported that approximately 29% of patients had inadequate CSU control (Dermatology Life Quality Index <5) after 16 weeks of omalizumab. Based on a meta-analysis of 7 randomized, placebo-controlled trials (n = 1312 patients), 36% achieved a complete response (UAS7 = 0) with omalizumab.⁷

In the literature and real-life practice, not all patients readily improve with omalizumab, likely reflecting a complex CSU pathophysiology not exclusively limited to immunoglobulin E–mediated degranulation events. An option for nonresponders is an increased omalizumab dosage of 450 mg to 600 mg, but the efficacy of this approach has not been formally examined. An analysis of the 3 largest CSU-omalizumab clinical trials revealed that the median time to achieve a UAS7 score of 0 ranged from 8 to 13 weeks; however, there was a subgroup of late responders at 24 weeks, potentially reflecting differences in anti-immunoglobulin E effects on basophils compared with mast cells.⁸

Thus, CsA may be considered the most potentially efficacious next-line option to exert immunosuppressive effects on T lymphocytes, eosinophils, basophils, and mast cells. In a recently published meta-analysis encompassing 909 patients, low-dose to moderate-dose (4–5 mg/kg/day) CsA controlled CSU at 4, 8, and 12 weeks with response rates of 54%, 66%, and 73%, respectively.⁹ Hypertension and abnormal serum creatinine levels occurred in 6.2% (very low dose), 12.8% (low dose), and 10.3% (moderate dose) of patients. Overall, the adverse event rate directly correlated with CsA dose and treatment duration.⁹ Similarly, in a prospective study (n = 27) by Serhat Inaloz et al,¹⁰ 70% of patients achieved a 25% reduction in UAS7 score with CsA dosage of 2.5 mg/kg/d for 4 weeks.

The patients included in this case series achieved complete CSU resolution at very low to low-dose CsA while continuing standard omalizumab therapy. We recognize the possibility that some of our patients could represent either as CsA responders (and omalizumab continuation was of minimal efficacy) or omalizumab late responders. The former theorized individuals (patient #2, 5, 6) had 24 or more weeks of omalizumab and responded to CsA within 1 to 2 weeks. Of note, no moderate-dose CsA was needed, suggesting that omalizumab possibly attenuated a need for higher CsA doses. Further studies are warranted to elucidate the mechanisms underlying omalizumab-refractory CSU and its optimal treatment.

To summarize, omalizumab with concomitant low-dose CsA administration is a safe and effective treatment for patients with omalizumab-refractory CSU. All CsA doses were less than 3.8 mg/kg/d, and the lowest effective doses were all considered very low dose except for 1 patient. Two-thirds of patients were able to taper off of CsA without CSU recurrence. Furthermore, most patients except 1 responded within 12 weeks of treatment. One developed hypertension managed with CsA dose reduction and an antihypertensive agent. Based on our limited experience, we support the alternative treatment regimen of concomitant low-dose CsA with close monitoring for

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Table 1
Patient Clinical Characteristics, Treatments Received, and Clinical Outcomes

Patient #	1	2	3	4	5	6
Age, sex	38, Female	50, Male	24, Female	33, Male	55, Female	47, Female
CU index—histamine release (%)	<16	79	55	>50		96
Biopsy results		Mixed (neut/eos) (on prednisone and omalizumab)	Eosinophilic predominant			Mixed (neut/eos) (on omalizumab)
Serum total IgE level (kU/L)	2		12			20
Duration of CSU before start of omalizumab (mo)	5	5	8	3	3	5
Daily systemic steroid use before omalizumab	Yes	Yes	No	No	Yes	No
Daily systemic steroid use during omalizumab without CsA	Yes	Yes	No	No	Yes	No
Weeks of omalizumab before CsA initiation	20	24	12	16	32	28
CsA starting dose (mg/kg/d)	1.1 (very low)	1.5 (very low)	2.5 (low)	2.8 (low)	3.0 (low)	3.7 (low)
CsA dose at clinical resolution, UAS7 = 0 (mg/kg/d)	2.2 (low)	1.5 (very low)	3.8 (low)	3.5 (low)	3.0 (low)	3.7 (low)
Lowest effective CsA maintenance dose, UAS7 = 0 (mg/kg/d)	0.7 (very low)	1.5 (very low)	1.9 (very low)	2.1 (low)	0.2 (very low)	0.4 (very low)
Time to clinical resolution on concomitant therapy (wk)	12	1	24	8	2	1
Total duration of CsA treatment (wk)	36	4	44	24	66 ^a	70 ^b
Random CsA serum level(s) (μg/L)	59/300/48/35/75/35/112	113	28/50	142/149/72/100	192/56/<25	70/74/<25/62/33/25
Most recent regimen	CsA Omalizumab Fexofenadine (03/2020)	Omalizumab ^c (09/2018)	Omalizumab ^d (2017)	Fexofenadine (03/2020)	Omalizumab Fexofenadine (03/2020)	CsA ^b Omalizumab Levocetirizine (03/2020)

Abbreviations: CsA, cyclosporine; CU, chronic urticaria; eos, eosinophilic; IgE, immunoglobulin E; kU, kilounits; neut, neutrophilic; UAS7, urticaria activity score over 7 days.

^aBreakthrough hives during taper requiring an increase in dose and then prolonged taper.

^bContinues to require intermittent very-low- to low-dose courses (<3 mg/kg/d).

^cPatient 1 was lost to follow-up 1 year after CsA cessation.

^dPatient 2 was lost to follow-up 2 months after CsA cessation.

patients who have not responded to at least 12 weeks of omalizumab. Formative studies are required to confirm the efficacy and safety of these findings.

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The clinical observation of a patient with common variable immunodeficiency diagnosed as having coronavirus disease 2019



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In December 2019, a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in the Wuhan region of China.¹ SARS-CoV-2, known to cause coronavirus disease 2019 (COVID-19), is a beta coronavirus with structural