Original Article

# Effectiveness of Hydroxychloroquine and Omalizumab in Chronic Spontaneous Urticaria: A Real-World Study

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***What is already known about this topic?*** The real-world effectiveness of hydroxychloroquine in treating patients with antihistamine refractory chronic spontaneous urticaria (CSU) is not well defined nor is its relative benefit compared with omalizumab.

***What does this article add to our knowledge?*** Hydroxychloroquine achieved complete control of urticaria in two-thirds of previously uncontrolled patients with CSU after at least 1 year of treatment versus 82% achieved with omalizumab, although clinical effectiveness was not apparent at 3 months in most patients.

***How does this study impact current management guidelines?*** Hydroxychloroquine should be strongly considered as an add-on treatment for patients with CSU uncontrolled with optimized doses of antihistamines and those unresponsive to second-line therapies including omalizumab.

**BACKGROUND: Chronic spontaneous urticaria (CSU) not controlled by optimized doses of antihistamines is referred to as refractory CSU. Add-on therapies recommended by guidelines include omalizumab, immunosuppressive, and anti-inflammatory agents.**
**OBJECTIVES: The objective of the study was to assess the real-world effectiveness of different add-on treatment options for refractory CSU in 2 large clinical practices.**
**METHODS: A retrospective chart review was conducted in 264 patients with refractory CSU not adequately controlled for ≥6 weeks with optimized doses of second-generation histamine-1 blockers. Omalizumab and hydroxychloroquine were the most frequently prescribed add-on therapies, allowing comparisons of clinical outcomes for these 2 agents. Complete response included absent or infrequent urticaria and patient satisfaction with treatment. Partial response was reduced hives, but requiring a second add-on therapy. Sustained response was complete response to an add-on therapy for ≥1 year.**
**RESULTS: Omalizumab add-on treatment was significantly more likely to be associated with a complete response versus hydroxychloroquine. Complete sustained response at 1 year was observed in 82% (111 of 134) of patients on omalizumab and 66% (73 of 111) on hydroxychloroquine as the first add-on therapy ($P < .01$). Patients with thyroid disease had a poorer response to add-on treatments (45% responded vs 63%; $P = .03$). In patients with incomplete responses to first add-on interventions (n = 45), 65% and 62% subsequently had complete responses to omalizumab and hydroxychloroquine, respectively.**
**CONCLUSIONS: Although omalizumab was superior, hydroxychloroquine achieved a complete response in two-thirds of treated patients. Given a favorable safety profile, hydroxychloroquine should be considered as an add-on treatment for refractory CSU.**  **(J Allergy Clin Immunol Pract 2022;■:■-■)**

***Key words:*** *Chronic spontaneous urticaria; Hydroxychloroquine; Omalizumab; Refractory*

Chronic spontaneous urticaria (CSU) is characterized by recurrent hives with or without angioedema, persisting for 6 weeks or longer.[1] The prevalence of CSU in the United States is estimated at 1%, affecting women twice as often as men.[2,3] The average duration is 2 to 5 years, although CSU symptoms can persist beyond 5 years in up to 30% of affected patients.[3]

Treatment guidelines recommend a stepwise approach to treatment of CSU. Initial treatment starts with second-generation H1 antihistamines. If symptoms persist, guidelines suggest increasing doses of H1 antihistamines by 2- to 4-fold, as well as adding H2 antagonists and leukotriene receptor

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*Abbreviations used*
*CSU- Chronic spontaneous urticaria*
*HCQ- Hydroxychloroquine*

antagonists.[4,5] Current evidence indicates that H1 antihistamines at higher than standard doses will adequately control symptoms in approximately 50% of patients, and a small number will get further benefit from the addition of H2 antihistamines and/or montelukast.[6,7] Approximately 25% of patients with CSU, whose symptoms are not controlled by the latter measures, are considered to have refractory CSU.[5,8,9] Treatment algorithms from published guidelines for chronic urticaria/angioedema have recommended additional therapies as either step 3 or step 4 treatment for antihistamine refractory CSU patients. Such agents include omalizumab as well as a variety of immunosuppressive drugs and anti-inflammatory agents.[5,10]

Omalizumab has proven efficacy and safety for refractory CSU.[11] Hydroxychloroquine (HCQ) is a less well investigated add-on therapy for patients with refractory CSU.[5] Data regarding the use of HCQ for refractory CSU are limited, although 1 study involving a small number of patients reported a significant improvement in quality of life.[12]

The purpose of this study is to compare the real-world effectiveness of different treatment options for refractory CSU in 2 large clinical practices. HCQ and omalizumab were the most frequently prescribed therapies for refractory CSU in these clinics, allowing the assessment of clinical outcomes for these 2 agents in many patients.

## METHODS

### Study design

The protocol for this retrospective chart review was reviewed by the University of Cincinnati institutional review board and received exemption from informed consent of patients with the understanding that all subjects were deidentified. Using electronic medical records of patients from 2 multiphysician Allergy and Immunology practices located in Cincinnati, Ohio, and Indianapolis, Indiana, we searched for patients diagnosed with CSU using International Classification of Diseases (Tenth Revision) code L50.1. Patient encounters occurred between March 2014 and November 2019, and data were gathered between December 2019 and November 2020. All patient data were reviewed in each chart by 2 independent reviewers for concordance.

The inclusion criteria included the presence of CSU with or without angioedema for at least 6 weeks and uncontrolled urticaria despite optimized doses of second-generation H1 antihistamines with or without montelukast, H2 antagonists, and doxepin. Patients with nonidiopathic chronic urticaria were excluded, including those whose urticaria was caused specifically by foods, medications, venom allergies, or other allergens.

Optimized doses of H1 antihistamines were not predefined, other than by standard treatment guidelines available at the time.[5] All patients received at least 2 times the standard dose of second-generation H1 antihistamines with or without H2-blockers, montelukast or doxepin. Uncontrolled CSU was defined as having at least 2 urticaria episodes per week despite treatment. There were 264 patients with CSU identified meeting the latter criteria. HCQ 200 mg by mouth twice daily or monthly subcutaneous omalizumab 300 mg was routinely offered to patients with CSU as initial add-on treatment with the understanding that patients would receive the alternative agent in the event of treatment failure. The choice of which to prescribe as initial add-on treatment was a shared decision by patients and physicians. Factors impacting these decisions included patients' preferences for oral versus parenteral treatment as well as the real cost of omalizumab to the patient. Other add-on agents administered to patients included cyclosporine, colchicine, dapsone, and sulfasalazine.

The primary outcome was response to treatment at 3 months after the initiation of the add-on treatment intervention. A complete response was defined as: (1) the absence of or infrequent occurrence of hives/itching after 3 months of therapy, and (2) the patient was satisfied and did not request additional treatment. A partial response was defined as: (1) a decrease in hives or itching, and (2) the patient expressed incomplete control of CSU symptoms and requested a different or additional therapeutic agent. No response to the add-on was defined as no improvement in hives or itching from the pre-treatment baseline.

Secondary outcomes evaluated included the need for a rescue course of oral corticosteroids after 3 months of therapy and sustained response. Sustained response was defined as a complete response to the most recent intervention for at least 1 year.

Responses were also assessed for second and third interventions in patients with CSU unresponsive to initial add-on treatments. In addition, compliance at 1 year based on physician documentation of the patient's reported compliance and the mean duration to complete response at 3 months were evaluated for various interventions.

Other data collected included history of comorbid thyroid and other autoimmune conditions, age of onset of CSU, sex, and duration of hives. Associations between these characteristics and response rates to various add-on drugs were evaluated.

### Statistical analysis

Descriptive statistics regarding the response rate to various treatment interventions at 3 months and 1 year were calculated using SAS software (Version 9.4; SAS Institute Inc, Cary, NC). Descriptive statistics for second and third interventions were also determined. $\chi^2$ tests were used to calculate $P$ values comparing the relationship between response rates for treatment interventions at both time points analyzed. $P < .05$ was statistically significant. $\chi^2$ and logistic regression tests were also used to determine the impact of various patient characteristics mentioned above on response rates.

## RESULTS

A summary of characteristics for patients included in the study can be found in Table I. Of 264 patients with refractory CSU, 83% were female. The mean age at the time of the first encounter in the allergy clinic was 44 years (range: 3-80 years). The median duration of urticaria from the time of diagnosis to the initiation of the first add-on intervention was 12 months (range: 3 months to 46 years). The initial or first add-on medications included omalizumab in 134 (51%) patients, HCQ in 111 (42%) patients, and a variety of other agents in 19 patients (7%), including colchicine, cyclosporine, sulfasalazine, and dapsone. There were no significant differences in baseline characteristics between patients who elected to receive omalizumab versus HCQ.

As shown in Figure 1, 154 (58%) patients achieved a complete response to the first intervention at 3 months, 77 (29%) had a partial response, and 33 (13%) reported no response. Patients receiving omalizumab were more likely to have a

**TABLE I.** Characteristics of patients treated with omalizumab and HCQ

| Characteristic | Omalizumab | HCQ | *P* value |
|---|---|---|---|
| Mean age | 44 y ± 13.19 | 45 y ± 12.10 | ns |
| Sex, n (%) | | | |
| Female | 110/134 (82) | 91/111 (82) | ns |
| Male | 24/134 (18) | 20/111 (18) | ns |
| With thyroid disease, n (%) | 36 (26.8) | 33 (29.7) | ns |
| Without thyroid disease, n (%) | 98 (73.1) | 78 (70.27) | ns |
| Other autoimmune condition, n (%) | 24 (17.9) | 18 (16.2) | ns |
| Previous treatment, n (%) | | | |
| Antihistamines | 134 (100) | 111 (100) | ns |
| Doxepin | 52 (39) | 40 (36) | ns |
| Montelukast | 105 (78) | 85 (77) | ns |
| Steroid burst | 70 (52) | 62 (56) | ns |

No significant differences were identified for age, sex, presence of thyroid disease, other autoimmune conditions, and previous treatment.
*HCQ*, Hydroxychloroquine; *ns*, not significant.

complete response at 3 months of treatment (110 of 134 [82%] patients) versus those initially treated with HCQ (42 of 111 [38%] patients) (Figure 2). A partial response was achieved in 20 (15%) patients on omalizumab and 50 (45%) on HCQ at 3 months (Figure 2). Among those responding at 3 months, the mean time to complete response with omalizumab and HCQ was 2.15 and 2.54 months, respectively, and not significantly different. After ≥12 months of therapy, an additional 31 of 38 (82%) patients with incomplete or no response at 3 months to HCQ reported a complete response to HCQ; 7 failed to respond. Thus, the complete response rate for HCQ improved from 38% at 3 months to 66% at 12 months ($P < .01$). One patient who did not report a complete response to omalizumab at 3 months did report a complete response by 1 year of therapy.

The sustained complete responder rate at 1 year was significantly greater for omalizumab (111 of 134 [82%] patients) compared with HCQ (73 of 111 [66%] patients) ($P < .01$). Of patients receiving HCQ as the first add-on therapy, 43% required rescue bursts of oral corticosteroids after 3 months of therapy, versus 32% of patients initiated on omalizumab ($P < .0001$). The overall self-reported compliance rate at 1 year was 85% for all interventions combined and was 86% and 91% for HCQ and omalizumab, respectively.

Of the 24 patients with either a partial or no response to omalizumab as the first intervention, 12 received HCQ as the second intervention. Eight of these (62%) experienced a complete response to HCQ by 12 months (Figure 3). Of the 69 patients who had a partial or no response to HCQ as the first intervention, 31 subsequently received omalizumab; 22 of these (65%) reported a complete response to omalizumab by 3 months (Figure 3). Thirteen patients failed to respond to both omalizumab and HCQ and then received a variety of third-line agents including colchicine (1), cyclosporine (8), sulfasalazine (3), and dapsone (1). The small numbers of patients treated with these agents did not allow for further analysis.

No significant associations were found between age, sex, and duration of CSU and complete response to the first add-on intervention (Table II). Patients with a personal history of thyroid disease were less likely to have a complete response to any add-on intervention (analyzed with all interventions combined) compared with patients without thyroid disease (45% vs 63%; $P = .03$, Table II). Patients with other autoimmune conditions (not including thyroid disease) were also less likely to have a complete response to any add-on intervention (analyzed with all interventions combined) compared with those without other autoimmune conditions (48% vs 60%; $P = .01$). There was no significant difference in response based on thyroid disease or other autoimmune conditions for omalizumab or HCQ when analyzed separately.

There were 7 patients diagnosed with primary immunodeficiency. There were no significant associations between responses to add-on interventions and the presence of an immunodeficiency disorder for all interventions together or for omalizumab and HCQ when analyzed separately. Seventy-three percent (195 of 264) of patients had received montelukast for CSU; there were no significant differences in responses to first add-on interventions based on montelukast status.

Most adverse effects of treatment were transient and included headache, fatigue, and injection site pain. No patient in either the omalizumab- or HCQ-treated groups discontinued the treatment because of adverse events. All HCQ-treated patients received baseline visual field testing before or during the first 3 months of treatment and annually thereafter. None developed retinopathy, an extremely rare adverse effect.

## DISCUSSION

This retrospective study of 264 patients from 2 clinical practices represents a large "real-world" experience with different add-on treatment options for refractory CSU. During the period these patients were evaluated and treated (2014-2019), the existing urticaria practice parameter did not specify omalizumab as a preferred first-line add-on agent for antihistamine refractory CSU, recognizing the potential benefits of other add-on agents (eg, HCQ and cyclosporin).[5] Because nearly all patients with CSU in these participating allergy practices received HCQ or omalizumab, we were able to compare the clinical effectiveness of these 2 agents. At 3 months, a complete response to omalizumab was identified in 82% of patients versus 38% of patients treated with HCQ. It is noteworthy that 1 year after starting the first add-on treatment, the omalizumab responder rate was unchanged, whereas that for HCQ had increased to 66%. The increase in the 1-year responder rate for HCQ observed in this study could be attributed to a slow onset of action of HCQ, like that observed in treated patients with rheumatoid arthritis and systemic lupus erythematosus.[13] In the latter disorders, a minimum therapeutic trial of 6 months is recommended because 95% steady-state concentrations of HCQ are not achieved until at least 6 months.[14] This could explain why 31 of 69 (45%) of partial or nonresponders to HCQ at 3 months became complete responders by 12 months.

To date, published reports of HCQ for refractory CSU are limited. A randomized placebo-controlled study of 18 patients with chronic urticaria demonstrated a significant improvement in quality of life after 12 weeks of treatment with HCQ, but no significant effect versus standard therapy alone on urticaria activity scores.[12] In an uncontrolled observational study of 19 patients with refractory CSU, 6 (33%) patients reported

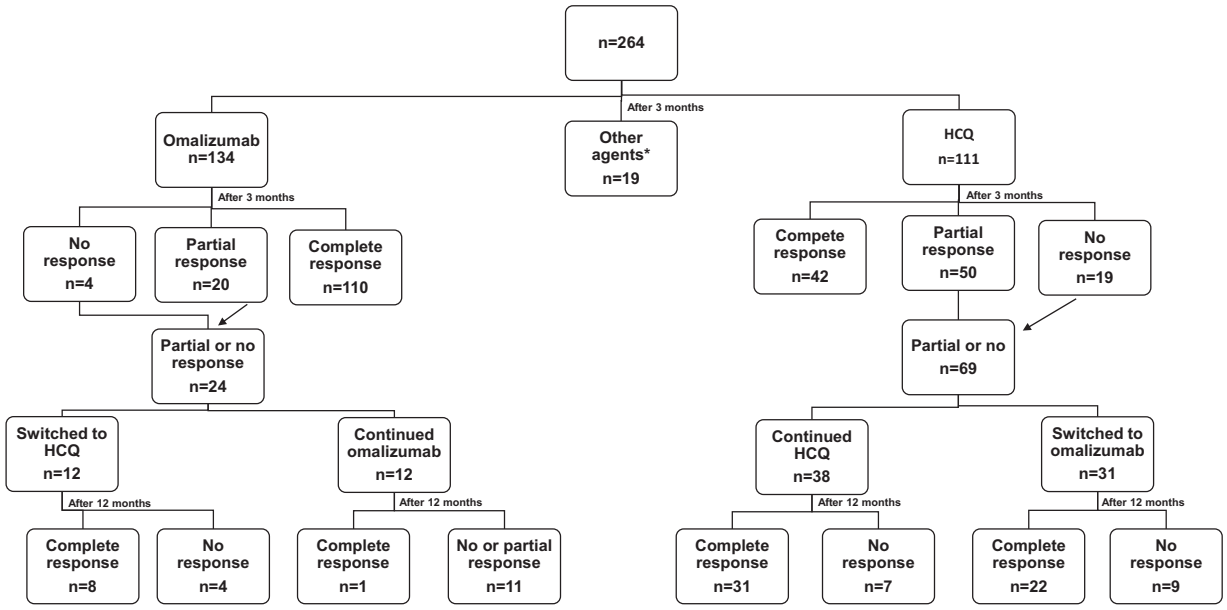


**FIGURE 1.** Flow diagram describing sequential add-on treatment interventions and resulting clinical responses as defined in the Methods section (ie, no response, partial response, complete response). *Other agents used as first add-on intervention included cyclosporine, sulfasalazine, colchicine, and dapsone. *HCQ*, Hydroxychloroquine.

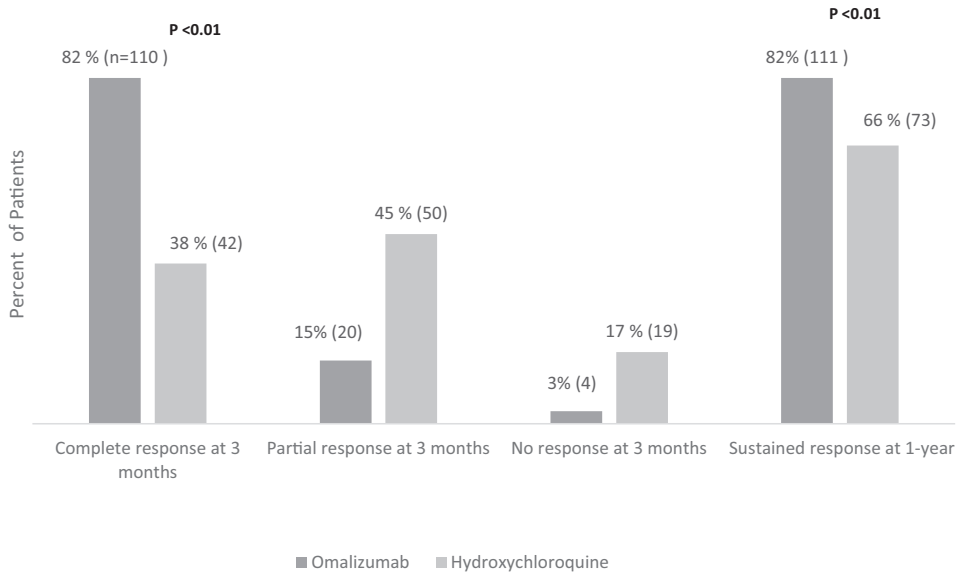


**FIGURE 2.** Responder rates expressed as percent (number) of treated patients to omalizumab and hydroxychloroquine (HCQ) in 245 patients with chronic spontaneous urticaria at 3 months and 1 year. Sustained response is defined as a complete response to the most recent add-on therapy for ≥1-year duration. There was a significantly greater complete response to omalizumab versus HCQ at 3 months and 1 year ($P < .01$).

complete resolution of urticaria, although the duration of HCQ treatment was not specified.[15] Thus, our study is unique because it provides effectiveness data on the largest reported cohort of patients who have received HCQ for refractory CSU. In addition, this is the only study comparing the effectiveness of omalizumab and HCQ for refractory CSU.

Another notable finding from this study is the good response to second add-on interventions in most patients. Eight of the 12 (62%) CSU patients with insufficient clinical responses to omalizumab were switched and responded well to HCQ, and 65% of HCQ nonresponders subsequently responded to omalizumab. This suggests that patients with refractory CSU

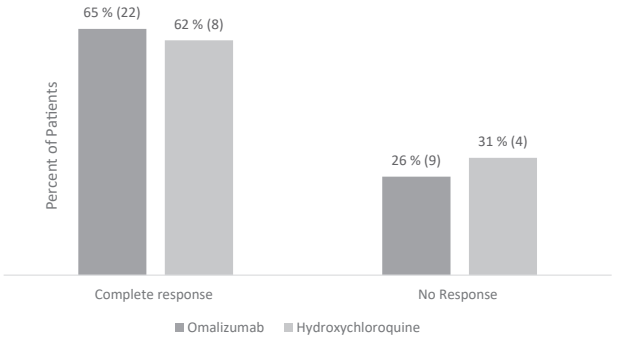


**FIGURE 3.** Responder rates after ≥12 months of therapy with second add-on interventions in 43 patients with incomplete responses to first add-on interventions expressed as percent (number) of treated patients. No significant differences in complete response rates were found between omalizumab and hydroxychloroquine.

unresponsive to either HCQ or omalizumab could respond well to the other agent.

The complete response rate to both omalizumab and HCQ at 3 months was significantly lower in patients with thyroid disease or other autoimmune conditions than in those without concurrent thyroid or other autoimmune conditions. Autoimmune diseases including Hashimoto's thyroiditis, pernicious anemia, vitiligo, diabetes mellitus type 1, Graves' disease, celiac disease, and rheumatoid arthritis are more prevalent in patients with CSU than in the general population.[16,17] In this study, 25% of patients had thyroid disease consistent with other studies.[18] The poorer response to add-in interventions for CSU in patients with autoimmune conditions, including thyroid disease, could have mechanistic implications for CSU and highlights the needs for development of more effective therapies for various subtypes of CSU in the future. We were unable to identify other clinical predictors of responsiveness to either of these treatments, although future studies could seek to evaluate candidate biomarkers associated with treatment outcomes. Another limitation of our study is that we did not explore whether patients whose CSU was exacerbated by nonsteroidal anti-inflammatory drugs might differentially respond to HCQ or omalizumab; this should be explored in future studies.

Putative mechanisms explaining the effect of HCQ in CSU are not well defined. HCQ is known to interfere with lysosomal function by increasing lysosomal pH.[19] In a study evaluating patients with mast cell disorders, Espinosa et al[20] found that HCQ modified mast cell granules by interfering with lysosome function, which led to an accumulation of nonfunctional tryptase. HCQ also reduced the expression of mast cell IL-8 and granulocyte-macrophage colony-stimulating factor.[20] Further studies are needed to better define the mechanism by which HCQ improves the control of CSU symptoms.

Both omalizumab and HCQ exhibited acceptable safety profiles in this study. Serial visual field testing in HCQ-treated patients did not identify retinal abnormalities. Rare anecdotal cases of arrhythmias, cardiac conduction abnormalities (eg, QTc interval prolongation), and cardiomyopathy have been associated with chloroquine and HCQ.[21] Current evidence, however, does not support a strong relationship between HCQ and risk for cardiac side effects. A recently published study in 2343 lupus patients treated with HCQ suggested that the drug reduced risk for cardiovascular events.[22] Because this was not the recommended standard of practice, HCQ-treated patients in this study were not routinely evaluated for adverse cardiac effects. Nevertheless, physicians prescribing these drugs should be aware of potential cardiac effects, particularly in patients who receive additional medications that prolong the QTc interval.

**TABLE II.** Characteristics of 264 patients with CSU refractory to antihistamines

| Characteristic | | Difference in response to first intervention |
|---|---|---|
| Age (y) | | |
| Mean | 44 | ns |
| Range | 3-84 | |
| Sex, n (%) | | |
| Female | 220 (83) | ns |
| Male | 44 (17) | |
| Duration of hives | | |
| Mean | 50 mo | ns |
| Median | 12 mo | |
| Range | 3 mo-46 y | |
| | Complete responders at 3 mo | |
| With thyroid disease (n = 69) | 31 (45% responded) | $P = .03$ |
| Without thyroid disease (n = 195) | 123 (63% responded) | |
| With other autoimmune condition (n = 42) | 20 (48% responded) | $P = .01$ |
| Without other autoimmune condition (n = 222) | 133 (60% responded) | |

*CSU*, Chronic spontaneous urticaria; *ns*, not significant.

The known safety of HCQ and lower cost relative to omalizumab makes HCQ an attractive alternative add-on therapy for refractory CSU. There are no national cost data available in the United States for direct comparison. Considering that CSU often requires years of treatment, the estimated annual cost difference in Canada of twice daily HCQ ($191 plus minimal costs associated with required annual retinal examinations) compared with monthly doses of 300 mg of omalizumab ($15,912) is compelling.[23] Thus, the overall cost burden incurred for managing refractory CSU could be diminished by an initial therapeutic trial of HCQ.

A major limitation of this study is its retrospective observational design. In addition, clinical response outcomes were based on global physician assessments rather than validated symptom scales such as urticaria activity scores. These limitations and the lack of a placebo treatment arm were mitigated by our ability to actively compare HCQ versus omalizumab, the benchmark add-on therapy for refractory CSU, in large cohorts of patients.

## CONCLUSIONS

A complete response to HCQ was achieved by 1 year in 66% of treated patients versus 82% treated with omalizumab. Because of its high responder rate and lower cost, HCQ is an acceptable alternative to omalizumab. The exact onset of action and

mechanism of action of HCQ in treating this disorder remains to be determined.

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