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Hydroxychloroquine: A Safe, Effective and Inexpensive Maintenance Therapy for Chronic Spontaneous Urticaria

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Abstract

Background: Chronic spontaneous urticaria (CSU) is an autoimmune skin disorder that lasts for >6 weeks and may last for years. It is a disabling skin disease that impairs quality of life. Set-up treatment with antihistamines, immunosuppressives, immune modulators and lately Omalizumab are expensive or have significant side effects. In this retrospective study, we describe our experience with the use of hydroxychloroquine (HCQ) as a maintenance therapy for those with severe forms of CSU after Corticosteroids (C) induction phase. **Patients and Methods:** 16 adult patients (aged 44 ± 7) with severe CSU for 5 ± 1 months, were included in the study. Eight patients had attacks of angioneurotic oedema. Their previous treatments were antihistaminic and short-courses of C. **Results**: After 2 weeks of remission with C and HCQ 200 mg twice daily, the dose of C was tapered down and discontinued by the end of the first month. The seven days Urticaria Activity Score decreased from 30 ± 3 to 6 ± 1 by the first month and remained low at 3 ± 1 by the end of 2 years of follow-up. Moreover, IgE levels and CRP had similar trends. Remission persisted after 37 ± 9 months of follow-up. **Conclusion:** HCQ is a safe, efficacious and inexpensive drug for the treatment of CSU.

Keywords

Autoimmune Disease, Chronic Spontaneous Urticaria, Corticosteroids, Hydroxychloroquine, Omalizumab

1. Introduction

Chronic spontaneous urticaria (CSU), formerly known as chronic idiopathic urticaria, is an autoimmune skin disorder. It is characterized by persistent and/or

recurrent daily attacks of fleeting itchy wheals, erythema and/or angioedema that lasts for ≥6 weeks [1]. Histologically, wheals are oedema in the upper dermis while angioedema is in the lower part of the dermis [2]. It is a disabling skin disease that impairs quality of life and affects several domains of health-related quality of life, such as activities of daily living, sleep, emotional and psychological well-being, and work productivity. While chronic urticaria affects 0.5% - 1% of the general population worldwide, CSU accounts for more than two-thirds of those cases [3]. It should be differentiated from a) inducible urticaria associated with local or systemic exposure to allergens or Angiotensin-converting enzyme inhibitors, b) vasculitis, and c) systemic autoimmune diseases [2]. CSU develops after mast cell activation followed by degranulation and release of histamine as the main mediator of symptoms alongside other cytokines and neuropeptides. The release of histamine from mast cells is a classic type I immediate reaction, yet mediated by autoantigens. Hence, and according to the EAACI/GA2LEN/WAO guidelines, a) second-generation non-sedating H1-antihistamines (AH2) used in quadruple doses are the first-line therapy and b) Omalizumab (Om) is for refractory cases [2]. Om is a monoclonal anti-IgE antibody that prevents IgE from binding to the FcεR1 receptor on mast cells and basophils, thereby inhibiting the release of inflammatory mediators [4]. Another less common cause of mast cell activation is the cross-binding of the Fc-receptors or the IgE molecules by IgG or IgM auto-antibodies, known as a type IIb reaction. Intracellularly the signal from the cross-binding is mediated through the Bruton tyrosine kinase pathway that activates nuclear factor kappa-light-chain-enhancer, nuclear factor of activated T cells, and activator protein-1 [2]. In the latter type, the response to AH2 and Om is limited [5]. In both types of CSU, high-dose Corticosteroids (C) are indicated in acute disease flare yet, due to their multiple long-term side effects, they should be tapered down and discontinued after remission by biological agents [6]. It should be noted that CSU does not lead to permanent organ damage, and it ultimately resolves in the majority of patients, with or without treatment within 2 - 5 years [1]. Unfortunately, the limited efficacy of anti-histamines II (AHII), multiple side effects of C as well as the cost and the parenteral mode of admiration biological agents are limiting factors in the treatment of such chronic and disabling disease. Hence, we conducted our study to assess the efficacy of hydroxychloroquine (HCQ) as an oral, inexpensive and relatively safe immunomodulator in the management of such disease.

2. Patients and Methods

In the past 5-years, a total of 16 patients with CSU, were treated in this prospective study. Patients were included if they had: a) severe CSU, b) duration ≤ 6 months to ensure previous treatment and clinical history, c) negative serology for autoimmune diseases, d) C-refractory disease *i.e.* previous treatments limited only to short-courses of AH2 and C yet with frequent remissions and relapses or C-dependency on C-dose reduction. CSU was defined by persistent and/or recurrent daily attacks of fleeting itchy wheals, erythema and/or angioedema that

lasted ≥6 weeks.

2.1. Study Design

On day 1 all patients had received a combination of a) Prednisone 1 mg/kg/day for 2 weeks followed by gradual tapering dose till discontinuation by the end of the 1st month, b) HCQ 200 mg twice daily. After the initial induction phase of 1 month, patients remained only on HCQ.

2.2. Periodic Assessment

Patients were seen weekly during the first month then on monthly basis for 3 months then every 2 months subsequently. In those visits, patients were assessed clinically for the severity of their CSU and side-effects of therapy especially with regards to fund us examination every 6 months. Laboratory investigations included complete blood count and serum estimates of sugar, renal, liver and lipid function tests and urine routines were done every 2 months.

2.3. Assessment of Severity of CSU

1) The severity of the disease and its response to therapy was assessed using the Urticaria Activity Score over 7 days (UAS7). It assesses the number of hives and the intensity of the itch once daily that generates a weekly score (UAS7), calculated as the sum of the daily number of hives score and the itch severity score over 7 days. UAS7 values range from 0 to 42, with higher values reflecting higher disease activity. UAS7 values were assigned to five score bands (0, 1 - 6, 7 - 15, 16 - 27, 28 - 42), reflecting urticaria-free to severe disease activity. Score bands include: (0) itch and hive-free and full treatment response, (1 - 6) well-controlled CSU and good response to treatment, (7 - 15) mild urticaria and lower response level, (16 - 27) moderately active CSU, and (28 - 42) severely active CSU [7].

2) Serum total IgE level by ELISA at time 0, 1 month, 2 years and end of follow-up. The latter is an immunoglobulin produced primarily by B-cells and plasma cells and is an important mediator of allergic disease [8].

3) C-reactive protein (CRP) at time 0, 1 month, 2 years and end of follow-up. The latter was used since it is a pentameric protein synthesized by the liver. It is an acute-phase reactant protein that is primarily induced by the IL-6 action on the gene responsible for the transcription of CRP during the acute phase of an inflammatory/infectious process [9].

2.4. Statistical Analysis

SPSS statistical package version 25 was used for data entry and processing. The p-value ≤ 0.05 was used as the cut-off level for significance. Since age, duration of CSU, UAS7-severity indices, and duration of follow-up were normally distributed, they were expressed as mean ± SD. Comparison of individual changes in UAS7 scores with time, following therapy, was done by t-test for repeated measures.

3. Results

A total of 16 patients fulfilled the clinical criteria for inclusion in the study, of whom 8 had recurrent angioneurotic oedema (Figure 1 & Figure 2). Patient's demographical profiles, UAS7 scores on entry and subsequent follow-up at 1 month then 2 years are summarized in Table 1. Eight (50%) patients were females. All were adults with (age at 44 ± 7 years). Their duration of CSU prior to our treatment was 5 ± 1 months and their disease was severe at a UAS7 score of 30 ± 3.

Response to Therapy

As shown in Table 1, all patients had significant responses to initial Corticosteroids and HCQ therapy. UAS7 scores decreased to 6 ± 1 ($p < 0.0001$). Moreover, HCQ therapy alone was able to prevent relapse on future follow-up (3 ± 1) which reflected progressive stability as compared to that in the first month ($p < 0.0001$). Such improvement and stability of disease were evident in a progressive decline in IgE and CRP levels at months 1 and 24. Moreover, IgE levels and CRP had similar trends.

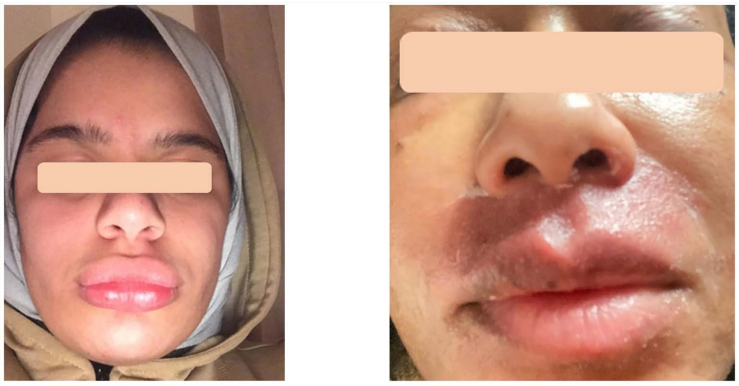

Figure 1. Photographs of 2 patients with severe angioneurotic oedema associated with severe chronic spontaneous urticaria.

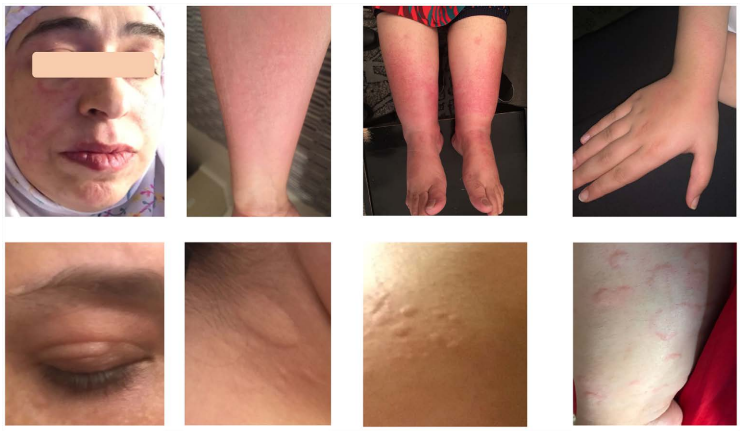

Figure 2. Photographs of multiple lesions in patients with severe chronic spontaneous urticaria.

Table 1. Demographical data on patients with CSU treated with hydroxychloroquine.

Patients' characteristics		(n = 16)
Demographical data:		
Gender (F/M)		8/8
Age (years)		44 ± 7
Duration of CSU (months)		5 ± 1
Duration of follow-up (months)		37 ± 9
Response to Hydroxychloroquine treatment*:		
Time 0		
	UAS7	30 ± 3
	IgE level	556 ± 60
	CRP	38 ± 9
Time 1 month		
	UAS7	6 ± 1
	IgE level	91 ± 5
	CRP	10 ± 1
Time 2 years		
	UAS7	3 ± 1
	IgE level	85 ± 4
	CRP	8 ± 1
End of follow-up:		
	UAS7	2.5 ± 0.5
	IgE level	83 ± 4
	CRP	7 ± 1

Abbreviations: CSU: chronic spontaneous urticaria, UAS7: urticaria activity score at 7 days. N.B.: Expression of age, UAS7, IgE, CRP, duration of CSU and follow-up, UAS7, as Mean ± SD. Normal range: IgE (<100 kU/L) and CRP (< 10 mg/L). *Significant improvement ($p < 0.0001$) from time 0 to 1 month and 2 years of follow-up, yet not between 2 years and the end of follow-up.

4. Discussion

CSU does not lead to permanent organ damage, and it ultimately resolves in the majority of patients, with or without treatment, within a few years. Hence, it is a) difficult to assess the impact of therapy versus its natural history, and b) long-term therapy with expensive drugs or those with serious adverse side effects is not warranted. In our study, all patients had definite and severe CSU that did not remit, with conventional therapy, for >6 months and hence, indicated long-term treatment. Hence, a) drugs with long-term side effects C, Calcineurin-inhibitors, Mycophenolate, dapsone, Sulfasalazine and costly one (Om) were avoided [10] [11]. In our study, HCQ was used, as a disease-modifying agent, for a minimum of 2 years based on its low cost as well as its documented efficacy and safety profile in rheumatological disorders [12]. Compared to Om, its

monthly cost is $149 versus $2446 [13]. Interestingly, our patients, with severe disease, had shown definite and rapid responses to our induction therapy with C-HCQ combination within 1 month similar to that achieved by Om [11]. Moreover, we proved that HCQ can be used safely as a sole maintenance therapy in C-refractory cases. In our study, we selected C-refractory cases and avoided, the rare, steroid-resistant cases that may require more aggressive immunosuppressive therapy [2] [14]. In our study, we confirmed the clinical response to HCQ (UAS7) with impressive improvements in both: a) serum total IgE level and b) CRP. The first plays a significant role in the immune system's response to allergens and parasites. Its initial high level correlates with response in type I CSU while those with low initial level reflect more of type II CSU [15]. On the other hand, CRP is an acute-phase reactant that is elevated in the presence of inflammation [16]. The mechanism of action of HCQ entails impairment of lysosome function in humans as well as plasmodia. Altering the pH of the lysosomes reduces low-affinity self-antigen presentation in autoimmune diseases and interferes with the ability of plasmodia to proteolyze hemoglobin for their energy requirements. Presently, it is being evaluated in bone marrow transplant patients to treat graft-versus-host disease as an immunosuppressive agent since it blocks T-cell activation *in vitro* via interfering with T-cell receptor-CD3 complex (TCR). The latter mediates recognition of antigenic peptides bound to MHC molecules, whereas the CD3 molecules transduce activation signals to the T cell [17]. In a concentration-dependent manner, HCQ inhibited anti-TCR-induced up-regulation of CD69 expression, a distal TCR signaling event. Proximal TCR signals, including inductive protein tyrosine phosphorylation, tyrosine phosphorylation of phospholipase C gamma1, and total inositol phosphate production, were unaffected by HCQ. Moreover, anti-TCR-crosslinking-induced calcium mobilization was significantly inhibited by HCQ, particularly at the highest concentrations tested (100 micromole/L) in both T-cell lines and primary T cells. Furthermore, HCQ, in a dose-dependent fashion, also reduced a B-cell antigen receptor calcium signal, indicating this effect may be a general property of HCQ. Inhibition of the calcium signal correlated directly with a reduction in the size of thapsigargin-sensitive intracellular calcium stores in HCQ-treated cells. Together, these findings suggest that disruption of TCR-crosslinking-dependent calcium signaling provides an additional mechanism to explain the immunomodulatory properties of HCQ [18].

5. Conclusion

HCQ is a safe and cost-effective treatment in C-refractory CSU.

Author's Contributions

Prof/Kamel El-Reshaid conceived the study, participated in its design, and drafted the manuscript. Dr. Shaima Al-Bader and Dr. Abdulla Al-Refaee participated in the study design, follow-up of patients and data collection and tabu-

lated the data. All authors read and approved the final manuscript.

Data Availability Statement

The data provided in the current review are available from the references.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Greaves, M. (2000) Chronic Urticaria. *Journal of Allergy and Clinical Immunology*, **105**, 664-672. https://doi.org/10.1067/mai.2000.105706

[2] Zuberbier, T., Abdul Latiff, A.H., Abuzakouk, M., Aquilina, S., Asero, R., Baker, D., *et al.* (2021) The International EAACI/Ga²Len/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis, and Management of Urticaria. *Allergy*, **77**, 734-766. https://doi.org/10.1111/all.15090

[3] Maurer, M., Weller, K., Bindslev-Jensen, C., Giménez-Arnau, A., Bousquet, P.J., Bousquet, J., *et al.* (2010) Unmet Clinical Needs in Chronic Spontaneous Urticaria. A GA²LEN Task Force Report. *Allergy*, **66**, 317-330. https://doi.org/10.1111/j.1398-9995.2010.02496.x

[4] Godse, K., Mehta, A., Patil, S., Gautam, M. and Nadkarni, N. (2015) Omalizumab—A review. *Indian Journal of Dermatology*, **60**, 381-384. https://doi.org/10.4103/0019-5154.160490

[5] McKeage, K. (2013) Omalizumab: A Review of Its Use in Patients with Severe Persistent Allergic Asthma. *Drugs*, **73**, 1197-1212. https://doi.org/10.1007/s40265-013-0085-4

[6] Yasir, M., Goyal, A. and Sonthalia, S. (2023) Corticosteroid Adverse Effects. StatPearls Publishing.

[7] Zuberbier, T., Aberer, W., Asero, R., Bindslev-Jensen, C., Brzoza, Z., Canonica, G.W., *et al.* (2014) The EAACI/GA² LEN/EDF/WAO Guideline for the Definition, Classification, Diagnosis, and Management of Urticaria: The 2013 Revision and Update. *Allergy*, **69**, 868-887. https://doi.org/10.1111/all.12313

[8] Ponsford, M.J., Klocperk, A., Pulvirenti, F., Dalm, V.A.S.H., Milota, T., Cinetto, F., *et al.* (2018) Hyper-IgE in the Allergy Clinic—When Is It Primary Immunodeficiency? *Allergy*, **73**, 2122-2136. https://doi.org/10.1111/all.13578

[9] Mouliou, D.S. (2023) C-Reactive Protein: Pathophysiology, Diagnosis, False Test Results and a Novel Diagnostic Algorithm for Clinicians. *Diseases*, **11**, Article 132. https://doi.org/10.3390/diseases11040132

[10] Holm, J.G., Ivyanskiy, I. and Thomsen, S.F. (2017) Use of Nonbiologic Treatments in Antihistamine-Refractory Chronic Urticaria: A Review of Published Evidence. *Journal of Dermatological Treatment*, **29**, 80-97. https://doi.org/10.1080/09546634.2017.1329505

[11] Kaplan, A., Ferrer, M., Bernstein, J.A., Antonova, E., Trzaskoma, B., Raimundo, K., *et al.* (2016) Timing and Duration of Omalizumab Response in Patients with Chronic Idiopathic/Spontaneous Urticaria. *Journal of Allergy and Clinical Immunology*, **137**, 474-481. https://doi.org/10.1016/j.jaci.2015.08.023

[12] Nirk, E.L., Reggiori, F. and Mauthe, M. (2020) Hydroxychloroquine in Rheumatic

Autoimmune Disorders and Beyond. *EMBO Molecular Medicine*, **12**, e12476. https://doi.org/10.15252/emmm.202012476

[13] Khan, N., Epstein, T.G., DuBuske, I., Strobel, M. and Bernstein, D.I. (2022) Effectiveness of Hydroxychloroquine and Omalizumab in Chronic Spontaneous Urticaria: A Real-World Study. *The Journal of Allergy and Clinical Immunology*: *In Practice*, **10**, 3300-3305. https://doi.org/10.1016/j.jaip.2022.08.051

[14] Kolkhir, P., Altrichter, S., Munoz, M., Hawro, T. and Maurer, M. (2020) New Treatments for Chronic Urticaria. *Annals of Allergy*, *Asthma & Immunology*, **124**, 2-12. https://doi.org/10.1016/j.anai.2019.08.014

[15] Ertas, R., Ozyurt, K., Atasoy, M., Hawro, T. and Maurer, M. (2017) The Clinical Response to Omalizumab in Chronic Spontaneous Urticaria Patients Is Linked to and Predicted by IgE Levels and Their Change. *Allergy*, **73**, 705-712. https://doi.org/10.1111/all.13345

[16] Kolkhir, P., Altrichter, S., Hawro, T. and Maurer, M. (2017) C-Reactive Protein Is Linked to Disease Activity, Impact, and Response to Treatment in Patients with Chronic Spontaneous Urticaria. *Allergy*, **73**, 940-948. https://doi.org/10.1111/all.13352

[17] Mariuzza, R.A., Agnihotri, P. and Orban, J. (2020) The Structural Basis of T-Cell Receptor (TCR) Activation: An Enduring Enigma. *Journal of Biological Chemistry*, **295**, 914-925. https://doi.org/10.1016/s0021-9258(17)49904-2

[18] Goldman, F.D., Gilman, A.L., Hollenback, C., Kato, R.M., Premack, B.A. and Rawlings, D.J. (2000) Hydroxychloroquine Inhibits Calcium Signals in T Cells: A New Mechanism to Explain Its Immunomodulatory Properties. *Blood*, **95**, 3460-3466. https://doi.org/10.1182/blood.v95.11.3460