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Hydroxychloroquine in the treatment of anti-histamine refractory chronic spontaneous urticaria, randomized single-blinded placebo-controlled trial and an open label comparison study

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KEY WORDS

chronic urticaria; anti-histamine refractory; hydroxychloroquine; randomized controlled trial; leukotriene receptor antagonist; montelukast

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Summary

Background. The management of anti-histamine refractory chronic spontaneous urticaria (CSU) has poorly defined therapeutic options. Some patients with CSU respond poorly to a fourfold increase in dosage of H1-anti-histamines treatment. **Aim.** The objective of this study was to determine the effect of an adjunct treatment of hydroxychloroquine (HCQ) on remission rate and reduction of urticarial symptoms. **Methods.** Sixty subjects with anti-histamine refractory CSU were randomly assigned to 400 mg of HCQ daily or placebo for 12 weeks in a single blind placebo controlled trial. In a second follow up trial, non-remission subjects were offered open-label HCQ in the placebo group or a leukotriene receptor antagonist (LTRA) in the HCQ group for 12 weeks. All subjects took 4 H1-anti-histamines tablets throughout the study. The endpoints measured were the urticarial symptom score (USS) and dermatology life quality index (DLQI). **Results.** Forty-eight patients (24 HCQ, 24 placebos) completed the randomized trial medication. Five of 24 on HCQ treatment but none on placebo had a remission at 12 weeks ($P = 0.01$). There was a low proportion of therapeutic failures occurred with 12-week HCQ treatment ($n = 5$) compared with placebo ($n = 14$, $P = 0.001$). After 12 weeks, USS and DLQI significantly improved in HCQ group over the placebo group. Forty non-remission subjects completed an open-label HCQ ($n = 22$) or LTRA ($n = 18$) comparison study. The remission rates on HCQ and LTRA were 22.72% and 5.55% at 12 weeks. However, no significant difference between the two groups in the therapeutic responses was observed. The mean USS on HCQ significantly decreased compared to the LTRA group, but there was no significant difference in DLQI. The adverse events reported were minimal and there were no subjects who discontinued the trial. **Conclusions.** This study suggests that HCQ is clinically effective as an adjunct treatment for CSU.

Introduction

The H1-antihistamines remain the first line of symptomatic treatment for chronic spontaneous urticaria (CSU). CSU typically responds to H1-anti-histamines therapy and the dosing can be increased to four-fold in cases of non-response (1). In

spite of the use of anti-histamines, some patients with CSU remain refractory to this therapy. An immunomodulatory drug may be added as an adjunct treatment to control urticaria symptoms, which include leukotriene receptor antagonist (LTRA), cyclosporine A and omalizumab (1).

Hydroxychloroquine (HCQ) is considered a disease-modifying anti-rheumatic drug, which is very well tolerated and inexpensive, and serious side effects are rare. However, its mechanism of action in the treatment of CSU is unknown, and the reports of the efficacy of HCQ treatment in CSU are limited. We designed a single-blind placebo-controlled randomized trial to evaluate the efficacy and safety of HCQ in patients with CSU, who did not respond to a four-fold increasing in dosing of H1-anti-histamines drugs. We also conducted a follow up open-label comparison study, to assess the efficacy of HCQ compared to LTRA to assess efficacy on the remission rate in the patients with CSU.

Materials and methods

Sixty adult patients who were diagnosed with CSU and did not respond to 4 tablets of H1-anti-histamines for 4 weeks at Allergy Clinic, Phramongkutklo Hospital, were invited to participate in this study. The exclusion criteria for this study included inducible urticaria and urticarial vasculitis. After a 2 week washout period, the subjects were randomly assigned to receive HCQ 400 mg/day or placebo adjunct treatment with 4 tablets of H1-anti-histamines drug for 12 weeks. Matched placebo pills were prepared by Department of pharmacy, Phramongkutklo Hospital. Only the patients were blinded. No increase in any other treatment for CSU was permitted for the duration of the study. The subjects with urticarial symptoms at the end of the study were recruited to an open-label comparison study and followed by a 2-week washout period. HCQ at a dose of 400 mg/day was administered in the former placebo group and montelukast (LTRA) at a dose of 10 mg/day was administered in the former HCQ-treated group for 12 weeks. This study was approved by the Institutional Review Board, Royal Thai Army Medical Department. All the subjects provided informed writ-

ten consent. Subject recruitment commenced in August 2010 and finished in September 2013.

Clinical evaluation, ophthalmic examination as well as the following investigations: erythrocyte sedimentation rate (ESR), thyroid autoantibodies, antinuclear antibody (ANA) and autologous serum skin test (ASST), were performed at baseline. The primary endpoint was remission rate. The secondary endpoints were urticarial responses that were assessed by the urticarial symptom score (USS) and dermatology life quality index (DLQI) (2,3). The response to treatment was assessed subjectively and recorded as remission (completely cured and discontinue medication at least 2 weeks), improved (urticaria symptoms improved during the treatment, and therefore reduce anti-histamine tablets but could not discontinue medication) or unchanged (urticarial symptoms still occurred). In follow-up visits symptoms and adverse events were assessed after taking HCQ every 2 weeks. The subjects had a second eye examination at the end of the study.

To compare baseline clinical characteristics between two groups, continuous data were analyzed by unpaired T-Test and others data were analyzed by Fisher's Exact Test. Comparison of remission rate and urticaria status was performed by Chi square test. Mann-Whitney *U* test was used to determine UAS and DLQI between groups. Data were analyzed using GraphPad Prism 6 (GraphPad Software, La Jolla, CA, USA). Significant levels were set at $p < 0.05$.

Results

A total of 55 subjects were randomized, 28 subjects in the HCQ group and 27 subjects in the placebo group (**figure 1**). Seven subjects did not complete the study, 4 subjects in the HCQ group and 3 subjects in placebo group. The baseline characteris-

Figure 1 - Schematic of study design.

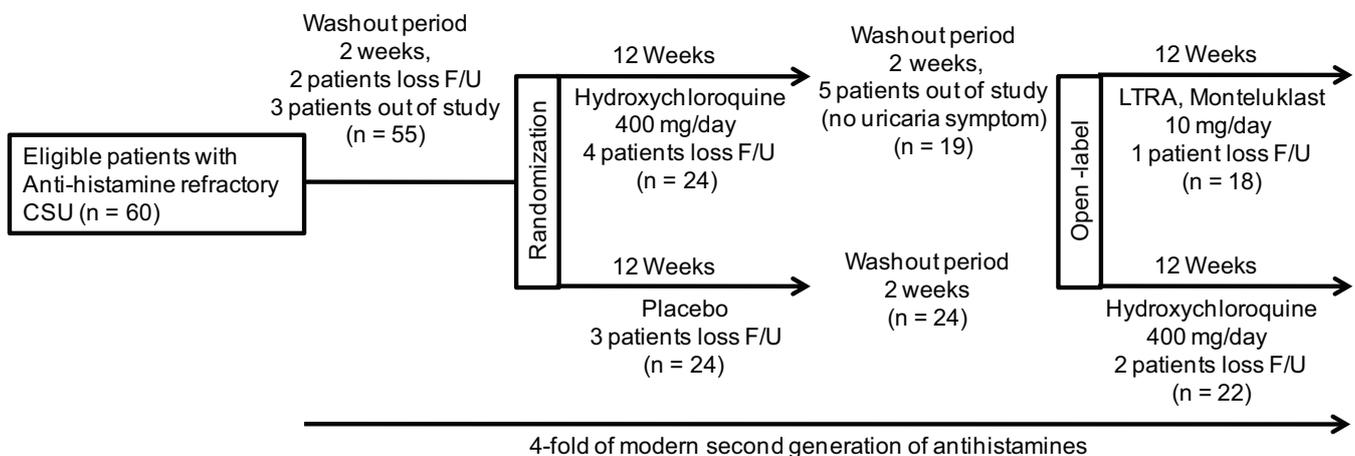
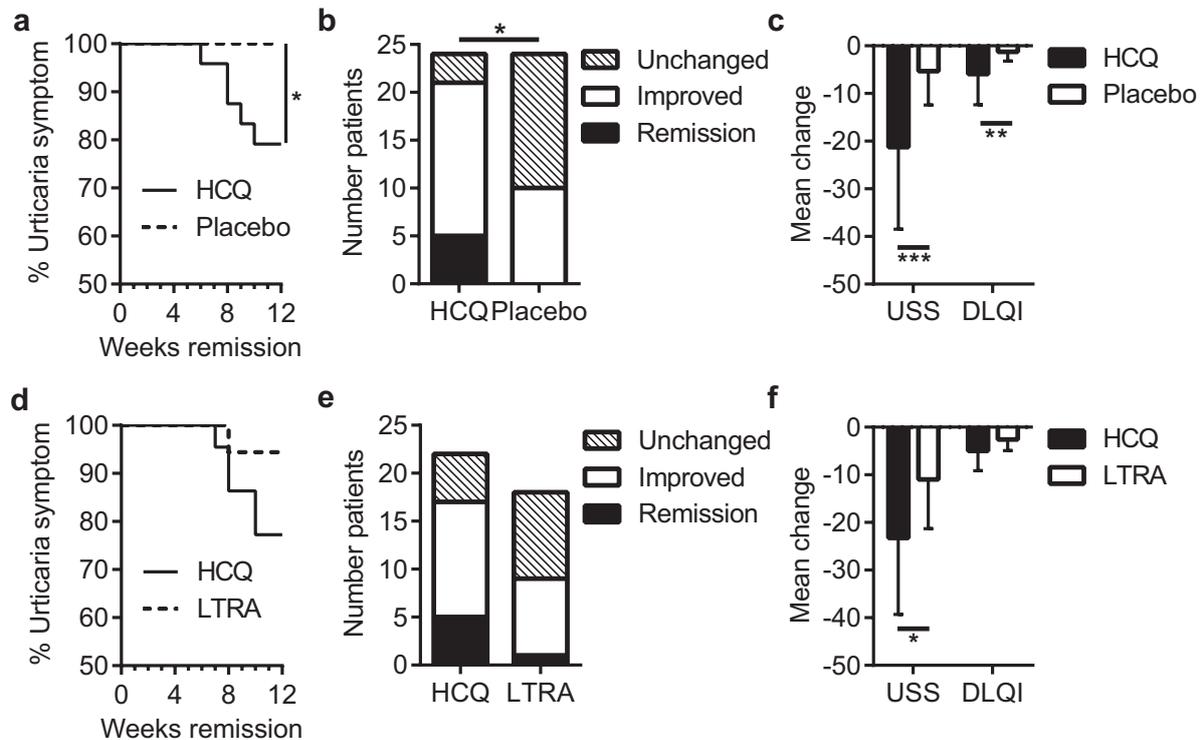


Table 1 - Baseline clinical characteristics of the subjects randomized to hydroxychloroquine (HCQ) or placebo.

	HCQ (n = 24) n (%)	Placebo (n = 24) n (%)	p-value
Sex, female	21 (87.50)	20 (83.33)	1.00
Age (Years, Mean \pm SD)	33.00 \pm 12.11	33.95 \pm 11.91	0.78
Duration (Weeks, Mean \pm SD)	21.71 \pm 19.53	24.291 \pm 23.41	0.68
ESR (Mean \pm SD)	18.29 \pm 12.49	17.62 \pm 6.80	0.81
Thyroid autoantibodies, positive	6 (25.00)	10 (41.66)	0.22
ANA, positive	10 (41.66)	11 (45.83)	0.77
ASST, positive	19 (79.16)	20 (83.33)	1.00
USS-baseline (Mean \pm SD)	45.54 \pm 11.25	43.42 \pm 12.26	0.53
DLQI-baseline (Mean \pm SD)	10.96 \pm 6.68	9.75 \pm 5.19	0.48

ESR, erythrocyte sedimentation rate; ANA, antinuclear antibody ASST, Autologous Serum Skin Test; USS, urticaria symptom score; DLQI, dermatology life quality index.

Figure 2 - Time to urticarial remission (a), proportion of urticarial responses (b) and reduction in urticarial symptom score (USS) and dermatology life quality index (DLQI) (c) in patients randomized to hydroxychloroquine (HCQ) or placebo. Inpatients with unchanged urticarial symptoms were followed by open-label HCQ or leukotriene receptor antagonist (LTRA). Time to urticarial remission (d), proportion of urticarial responses (e) and reduction in USS and DLQI (f) in patients treated with HCQ or LTRA. F/U, follow-up, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.



tics of the two groups are shown in **table 1**. There was no significant difference in these baseline characteristics between the two groups. Five of 19 subjects (20.83%) on HCQ but none on placebo achieved remission at 12 weeks ($p = 0.01$) (**figure 2a**). Sixteen subjects in the HCQ group and 10 subjects in the placebo group revealed clinical improvement. There was a significantly lower proportion of therapeutic failures in the subjects treated with HCQ, $n = 5$ than in those who received placebo, $n = 14$ ($p = 0.001$) (**figure 2b**). After 12 weeks, the severity score was significantly improved by HCQ treatment ($p = 0.0001$), and these patients experienced significant improvement in DLQI scores with HCQ compared with the placebo ($p = 0.004$) (**figure 2c**). In a follow up study, forty-three subjects with urticarial symptoms, 24 subjects with HCQ and 19 subjects with LTRA continued in the open-label comparison study. Three subjects did not complete the study, 2 subjects in the HCQ group and 1 subject in the LTRA group. After the 2-week washout period, the mean USS scores (38.54 ± 12.30 and 34.77 ± 10.90) and DLQI scores (8.68 ± 3.51 and 7.83 ± 2.72) between the HCQ and LTRA group were not significantly different. The HCQ group showed a higher rate of remission, 22.72% compared to the LTRA group, 5.55%, although significance was not reached (**figure 2d**). The difference between HCQ and LTRA in the urticarial responses was not statistically significant either (**figure 2e**). However, a significantly greater reduction in symptom score was observed at 12 weeks in the HCQ group compared to LTRA group ($p = 0.01$) (**figure 2f**). Five subjects of the total 46 (10.86%) who were HCQ-treated reported adverse events. One subject had a problem with a severe headache at the first week of taking HCQ. Four subjects felt their skin were darker. However, none of the subjects complained about eye problem and all of the subjects had passed their eye examination at the end of the study. One subject in the placebo group had dizziness and two subjects reported a gastrointestinal disturbance. No subject in LTRA group was reported as an adverse event.

Discussion

We reported that the adjunct HCQ treatment in addition to primary therapy with the fourfold dose of H1-anti-histamines is more effective than placebo and LTRA on remission rate, and in reducing the severity of CSU after 12 weeks. Moreover, no serious side effects were reported from this study. There has been only one placebo controlled trial previously by Reeves et al. reported in 2004 (4). They showed the efficacy of HCQ therapy in chronic autoimmune urticaria, where patients treated with HCQ achieved significantly more improvements in quality of life than the placebo group at 12 weeks. However, they did not report the remission rate in the HCQ group. In this study, we reported a low remission rate in the HCQ group which might be due to a high rate of positive ASST (autologous

serum skin tests) among subjects. Patients with the positive autologous skin test had a lower remission rate compared with those who had negative skin test (5,6). The rate of remission over 2 years in the negative, positive ASST, and both positive ASST and autologous plasma skin test (APST) groups, were 81.1%, 62.3% and 46.1%, respectively (6). Moreover, negative ASST had the chance to achieve remission more than positive ASST (OR, 3.97; 95% CI, 1.47-9.43; $p = 0.001$) (6). However, in the previous study, the subjects were not only treated with HCQ, they also received other third line therapy (eg, dapsone, cyclosporine and leukotriene antagonist). Low-dose cyclosporine A in the treatment of severe CSU achieved remission 26-68% (7,8). Vena GA et al reported, after 16 weeks, symptoms scores significantly improved with cyclosporine A treatment group more than placebo, but no patients achieved full remission, and 6% of patients led to discontinuation of treatment due to adverse events (9). The adverse side effects of cyclosporine A require constant monitoring, including its effects on blood pressure and renal function. Omalizumab (anti-IgE) is a very effective treatment for CSU, but the cost of the treatment is expensive for routine use in developing countries (10). The limitation of the study was a high incidence of withdraws, and we conducted the non-randomized controlled study to assess the efficacy of HCQ and LTRA.

In summary, HCQ was a useful short-term treatment for the patient with CSU who were refractory to a fourfold increase in dosage of H1-anti-histamines treatment. The benefits of HCQ include enhancing remission of patients, diminishing urticarial symptoms, and safety.

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