

ORIGINAL ARTICLE

Impact of hydroxychloroquine therapy on chronic urticaria: chronic autoimmune urticaria study and evaluation

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Abstract

Background: Chronic urticaria (CU) imposes profound impairment on quality of life. Up to 60% of idiopathic CU is associated with autoimmune phenomena, and may respond to immunomodulation. Hydroxychloroquine offers potential efficacy for CU and is relatively benign compared with most other therapeutic approaches.

Objective: The aim of the chronic autoimmune urticaria study and evaluation was to evaluate the efficacy of hydroxychloroquine in patients with chronic idiopathic urticaria.

Methods: Twenty-one patients referred to the Immunology and Allergy Unit at John Hunter Hospital, New South Wales, Australia, with idiopathic CU were randomised to receive treatment with standard urticaria therapies (corticosteroids, H₂-antihistamines, H₁-antihistamines, doxepin) with or without hydroxychloroquine. Markers of autoimmunity, thyroid disease and mast-cell autoreactivity (autologous serum skin-prick testing (ASPT)) were assessed. Measures of urticaria control were compared at baseline and at 12 weeks for

the 18 individuals who completed the study. These included urticaria scores, medication scores and quality-of-life indices.

Results: The hydroxychloroquine-treated group achieved significant improvements in quality of life as assessed by the global symptom severity score and the LAMY-7 (a quality of life index designed by Lamy, 7th revision) at 12 weeks ($P < 0.01$ and $P < 0.05$, respectively). No significant treatment effect on medication requirements or urticaria score was detected, although differences between treatment groups approached statistical significance for urticaria score and medication requirements ($0.05 < P < 0.10$). ASPT-reactivity did not correlate to hydroxychloroquine-responsiveness. Hydroxychloroquine was well tolerated.

Conclusion: Immunomodulation with hydroxychloroquine is safe and appears to offer some efficacy as an intervention in CU. (Intern Med J 2004; 34: 182–186)

Key words: chronic urticaria, hydroxychloroquine, autologous skin testing.

INTRODUCTION

Chronic urticaria (CU) imposes profound impairment on quality of life.¹ Most cases of CU have been labelled idiopathic, with no clear cause being definable. The frequent association between CU and thyroiditis, and the fact that 9% of lupus patients first present with CU, provided the first clues to an autoimmune aetiology in CU. It has since been established that up to 60% of idiopathic CU could be associated with autoimmune phenomena,² with measurable serum antibodies to the mast-cell surface high-affinity immunoglobulin E (IgE) receptor,³ or, less commonly, to the IgE molecule itself.⁴ Anti-FcεRI antibodies (antibodies to the high-affinity

IgE receptor) may be pathogenic, triggering mast-cell activation and degranulation and hence urticaria. This proposed autoimmune aetiopathogenesis of CU has prompted trials of immunomodulation for the condition, including the use of corticosteroids, cyclosporin-A, intravenous immunoglobulin and plasmapheresis.⁵ Hydroxychloroquine offers potential efficacy for CU and is relatively benign compared with most other therapeutic approaches.^{6,7} The aim of the chronic autoimmune urticaria study and evaluation (CAUSE) was to evaluate the efficacy of hydroxychloroquine in patients with chronic idiopathic urticaria.

METHODS

Patients

Patients referred to the Immunology and Allergy Unit at John Hunter Hospital, a large tertiary referral teaching hospital in New South Wales, Australia, between January and December 2001 with CU were invited to participate in the present study if they had a history of urticaria occurring two or more times per week over a

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continuous period of more than 6 weeks. They needed to be older than 18 and able to give informed consent, and women of child-bearing age were required to take contraceptive measures. Before qualifying for recruitment, patients with other underlying aetiologies were excluded (thyroid disease, vasculitis, lupus and related disorders, food intolerance, specific allergies). Patients were also excluded from the study if they were already receiving hydroxychloroquine or any other antimalarial agent, or if there was a history of previous toxicity from 4-aminoquinoline compounds. The trial protocol was reviewed and approved by the Hunter Area Research Ethics Committee. Patients provided written informed consent.

Study design

Patients were randomly assigned to receive hydroxychloroquine or placebo for 12 weeks, in addition to their other symptomatic urticarial therapies (corticosteroids, H2-antihistamines, H1-antihistamines, doxepin). Treatment was blinded by administering treatments within opaque capsules. Medication counts on pharmacy-supplied dispensing canisters were performed at 4 and 12 weeks. At baseline, the following investigations were undertaken: full blood count, erythrocyte sedimentation rate, C-reactive protein, urea, creatinine, electrolytes, liver-function tests, creatinine kinase, thyroid-stimulating hormone, antibodies to gastric parietal cells, gliadin, transglutaminase and thyroid antibodies and antinuclear antibody. Baseline muscle strength and ophthalmological appearances were also recorded. After 48 h free of antihistamines, patients underwent autologous serum skin-prick testing (ASPT). ASPT was performed according to the method of Grattan: briefly, 5-mL venous blood was obtained under aseptic conditions and centrifuged at 1000 *g* for 15 min.⁸ Intradermal testing was performed with 50 µL of the patient's centrifuged serum and the mean diameter of the resulting weal was read at 15 min. The following baseline markers of urticarial control were collected: global symptom severity score (GSSS, a visual analogue scale assessing the severity of itch over the previous three days); urticaria scale (US, a semiquantitative assessment of urticarial severity, calculated as the sum of the products of hive numbers, hive size) (graded 1 (mild) through to 3 (severe)) and itch intensity (visual-analogue scale) over a 1-month period following each study visit); and two validated quality-of-life indices, the LAMY-7⁹ and the short form (SF)-12.¹⁰ A medication score was calculated by adding weighted scores for dosages of each of the major therapeutic families, with weighting increased for medications associated with a significantly heightened potential for short- or long-term toxicity. The prevalence of side-effects associated with each therapy was reviewed through Medline and Micromedex searches, and a risk assessment index (RAI) was calculated for each agent as follows: $RAI = 6 \times (\text{average of severe side-effect risks}) + 3 \times (\text{average of moderate side-effect risks}) + (\text{average of mild side-effect risks})$. Weights derived from these calculations were applied as follows: H2-blockers (ranitidine 150 mg twice daily or equivalent; 0.8); non-sedating

H1-blockers (Claratyne (Schering-Plough, Sydney, Australia) 20 mg/day, Telfast (Aventis Pharma, Sydney, Australia) 240 mg/day or equivalent; 1.0); less-sedating H1-blockers (cetirizine 20 mg/day; 1.5); sedating-combined antihistamines (doxepin 20 mg/day, Phenergan (Wyeth Australia, Sydney, Australia) 50 mg/day or equivalent; 2.0); and corticosteroids (prednisone 20 mg/day or equivalent; 4.0). If control of itch and urticaria were satisfactory on further assessment at 2 weeks (by telephone) and during subsequent visits, graded reduction of medication was sequentially recommended as follows: prednisone was weaned gradually over 2 weeks; doxepin was weaned over 2 weeks; cetirizine was reduced from 20 mg/day to 10 mg/day, or ceased if the current dose was 10 mg/day; non-sedating H1-blockers were ceased; and ranitidine was discontinued. Follow-up assessment for hydroxychloroquine toxicity included repeat blood count, biochemistry, liver function testing and creatinine kinase at 4 and 12 weeks, with repeat muscle-strength testing and ophthalmological review occurring on study completion at 12 weeks.

Statistical analysis

The sample size of 10 patients per group was selected to provide a greater than 75% power for detecting a treatment difference in favour of hydroxychloroquine with a one-sided Type I error of less than 0.025. Power calculations assumed a placebo response rate of 35% for the composite for quality-of-life indices and a hydroxychloroquine response rate of 70%. All analyses were performed on an intention-to-treat basis. The statistical testing used to assess the primary end-points was a Student's *t*-test (Intercooled Stata 7.0; Stata Corporation, College Station, TX, USA).

RESULTS

Twenty-one patients referred to the John Hunter Immunology and Allergy Clinic for assessment of chronic urticaria were recruited to the study. There were three drop-outs: two as a result of non-attendance at follow-up review and one because the patient was withdrawn from the study as a result of the development of thrombocytopenia during the trial (later shown to be related to intercurrent Epstein-Barr virus infection). The mean age was 38.2 years and the male : female ratio was 5:1. Of the 18 patients who completed the study, 35% were positive on ASPT. Other baseline characteristics of the two groups appear in Table 1. There was no significant difference between the two groups in terms of age, gender ratio, ASPT positivity, baseline medication needs and baseline urticarial control as assessed by GSSS, US, LAMY-7 and SF-12.

The hydroxychloroquine-treated group achieved significant improvements in quality of life as assessed by the GSSS and the LAMY-7 at 12 weeks (Fig. 1). Changes in mean scores with corresponding confidence intervals are tabulated in Table 2. No significant treatment effect on medication requirements or urticaria score was detected, although differences between treatment groups approached statistical significance for urticaria score and medication requirements.

Table 1 Baseline characteristics

	Placebo (<i>n</i> = 9)	Hydroxychloroquine (<i>n</i> = 9)
Medication score	2.8	1.5
Haemoglobin (g/L)	141.7	142.0
ESR (mm/h)	6.1	11.4
CRP (mg/L)	5.2	5.5
Autoimmune diathesis [†]	4	6
ASPT-positive	3	3
TSH (mIU/L)	1.8	1.6
Thyroid antibody-positive	0	3
Vitamin B12 (pmol/L)	265	221
Gastric parietal cell antibody-positive	2	1
ANA-positive	3	3
C3 (g/L)	1.16	1.38
C4 (g/L)	0.26	0.27
Global symptom score	5.5	7.9
SF-12 score	19.1	24.1
LAMY-7	6.6	5.3
Urticaria score	66.8	98.3
Years of urticaria (mean)	1.5	1.7

[†]Assessed by the coexistence of antibodies to thyroid microsomal antigen, thyroglobulin antibodies, gastric parietal cell antibodies or antinuclear antibodies. ANA, antinuclear antibody; ASPT, autologous serum skin-prick testing; C, complement component; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Lamy-7, Lamy 'smiley faces' quality of life index; SF-12, short form 12 quality of life index; TSH, thyroid-stimulating hormone.

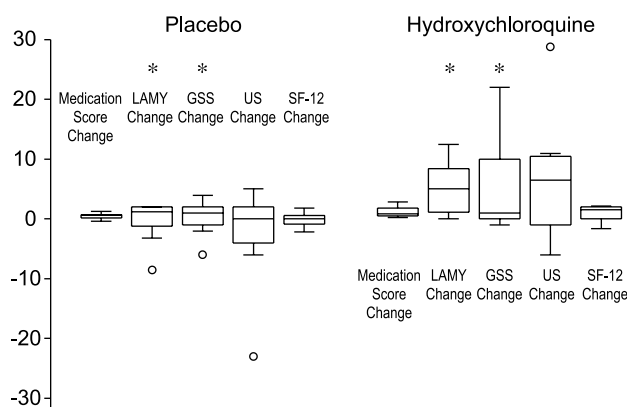


Figure 1 Changes in medication and symptom scores. (*) Significant improvement with hydroxychloroquine versus placebo.

The correlation between the presence of an autoimmune diathesis and ASPT positivity was poor, with a concordance rate of 41%; three patients were ASPT-positive without other autoimmune markers and seven patients with an autoimmune diathesis were ASPT-negative. No significant toxicity from hydroxychloroquine treatment was demonstrated during the course of the trial. ASPT reactivity and the presence of an autoimmune diathesis were associated with significant hydroxychloroquine responsiveness ($P < 0.05$) in terms of the GSSS, but not in terms of other quality-of-life markers, medication requirements or urticarial scores.

DISCUSSION

The use of hydroxychloroquine was associated with a significant improvement in the quality of life of individuals suffering from chronic urticaria in the present study. The small sample size of the study limited its power to

Table 2 Mean score changes

	Hydroxychloroquine mean change (95% CI)	Placebo (<i>n</i> = 8) mean change (95% CI)	Significance
Medication score	0.53 (−0.51 to 1.57)	1.20 (−0.72 to 3.12)	0.05–0.10
Global symptoms	0.4 (−7.4 to 6.6)	5.2 (−3.6 to 14)	$P < 0.01^{\dagger}$
SF-12 (physical)	2.01 (−22.27 to 18.25)	3.73 (−15.51 to 8.05)	0.1–0.2
SF-12 (mental)	9.07 (−20.31 to 38.45)	4.58 (−10.66 to 19.82)	0.1–0.2
LAMY-7	2.9 (−19.7 to 13.9)	6.9 (−14.9 to 28.7)	$P < 0.05^{\dagger}$
Urticaria score	1.36 (−2.35 to 2.25)	1.66 (−1.92 to 2.25)	0.05–0.10

[†]Statistically significant effect of hydroxychloroquine therapy. CI, confidence interval; Lamy-7, Lamy 'smiley faces' quality of life index; SF-12, short form 12 quality of life index.

detect significant changes in other parameters, such as medication requirements.

Autoimmune chronic urticaria (AICU) is emerging as a dominant cause of CU, potentially explaining up to 60% of previously idiopathic cases. Although hydroxychloroquine has been proposed as a promising approach to improving disease control in CU patients,⁶ few trials of this therapy have been performed. The present study found no significant effect of hydroxychloroquine on urticarial activity and medication requirements.

The CAUSE study's power to detect a significant difference between treatment groups was compromised by patient drop-outs as a result of non-compliance and intercurrent events. Hydroxychloroquine treatment was associated with an improvement in quality of life as assessed by the GSSS. The preferential effect on global symptoms might reflect a Type I (false positive) error because of small patient numbers. However, there was a detectable improvement in the hydroxychloroquine-treated group, as measured by the medication score and urticaria score, which fell just short of statistical significance ($P = 0.05-0.10$), implying the presence of a true treatment effect. Moreover, an effect of hydroxychloroquine on non-urticarial factors impacting on pruritus and well-being cannot be excluded, and could explain the discrepancy between global and urticaria-specific improvement. This possibility is buttressed by the demonstration of benefit offered by hydroxychloroquine in terms of energy levels and well-being in chronic autoimmune conditions, such as rheumatoid arthritis and lupus,¹¹ with such effects demonstrated to be partially independent of improvements in arthritis control.^{12,13}

There is a temporal lag between introduction of hydroxychloroquine therapy and symptomatic benefit, which has been reported to average between 6 and 24 weeks.¹⁴ Although latency of treatment efficacy might be more prolonged on occasions, the experience at the Immunology and Allergy Unit at John Hunter Hospital is that the success or otherwise of a therapeutic trial of hydroxychloroquine can be assessed after 12 weeks, and this is supported by other published reports.¹⁵ Therefore, the 3-month duration of patient follow up in the present study was appropriate and was unlikely to have led to underestimation of the efficacy of hydroxychloroquine.

ASPT could serve as a surrogate marker for the presence of the Fc ϵ RI antibodies believed to be implicated in the pathogenesis of AICU. Autoimmune processes are said to explain up to 60% of idiopathic urticaria, although the prevalence of AICU as assessed by ASPT was only 35% in the present study. There was no clear correlation between ASPT results and hydroxychloroquine responsiveness in the present study, although the assessment of mast-cell-directed autoimmunity through other methodologies, such as Fc ϵ RI antibody, enzyme-linked immunosorbent assay or western blot testing, might more accurately determine the presence of AICU.

Hydroxychloroquine appears to exert its immunomodulatory effects on lupus and related conditions

partly through alkalinisation of cytoplasmic vacuolar contents, altering the cleavage of peptides in preparation for binding and presentation by major histocompatibility complex class II molecules. Through its effects on the handling of self-antigens, hydroxychloroquine has been successfully used in managing a number of manifestations of autoimmune disease, including the fatigue, rash and arthralgias of lupus, rheumatoid arthritis, the sicca symptoms of Sjögren's syndrome¹⁶ and the thrombophilia of the phospholipid antibody syndrome.¹⁷ The general evidence of safety for hydroxychloroquine is supported by the present study. Indeed, a growing number of ophthalmological experts argue that routine screening for evidence of hydroxychloroquine retinal toxicity is no longer needed, in view of the extreme rarity of this complication at the dose used in the present study.^{18,19} Hydroxychloroquine's relative safety and freedom from side-effects makes it an attractive option to reduce or abolish requirements for other more toxic agents, particularly corticosteroids.

In conclusion, immunomodulation with hydroxychloroquine is safe and appears to offer some efficacy as an intervention in CU. Given its generally excellent safety profile, a trial of hydroxychloroquine could be indicated in cases of chronic urticaria, especially when refractory to other modalities.

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