

[ORIGINAL ARTICLE]

Continuation Rate, Safety and Efficacy of Hydroxychloroquine Treatment in a Retrospective Cohort of Systemic Lupus Erythematosus in a Japanese Municipal Hospital

Yohei Hosokawa and Hiroshi Oiwa

Abstract:

Objective We investigated the continuation rate, safety and efficacy of treatment with hydroxychloroquine (HCQ) in a retrospective cohort of systemic lupus erythematosus (SLE) in a Japanese municipal hospital.

Methods All of the patients with SLE who started treatment with HCQ were included in this study. A retrospective chart review was performed. Our primary outcomes were the continuation rate of HCQ treatment for 1 year and adverse events (AEs) during the treatment. We also investigated the efficacy of HCQ treatment in cases in which treatment with immunosuppressive therapies remained unchanged for the preceding six months.

Results Forty-seven patients with SLE were included in this study. Twenty-five patients (53.2%) had AEs. Eleven (64.7%) of the 17 patients who tried the readministration of HCQ could continue HCQ treatment. The continuation rate of HCQ for a period of 1 year was 78.3% (36 of 46 patients). The development of cutaneous lesions was the most frequent adverse event (25.5%) followed by gastrointestinal symptoms (8.5%). In the 16 cases in which the immunosuppressive therapies remained unchanged for at least six months prior to starting HCQ treatment, the SLE disease activity index, anti-DNA antibody, immune complex, and serum complement activity significantly decreased over a period of 1 year, while the prednisolone dose significantly decreased.

Conclusion The continuation rate of HCQ treatment was high in an SLE cohort of a Japanese municipal hospital. Although more than half of the patients experienced AEs, the readministration of HCQ was often successful. HCQ treatment provided benefits regarding the clinical and immunological findings in Japanese patients with SLE, which would likely lead to glucocorticoid tapering.

Key words: systemic lupus erythematosus, hydroxychloroquine, continuation rate, safety, Japanese, cohort study

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Introduction

Treatment with hydroxychloroquine (HCQ), as well as glucocorticoid therapy, is included in the standard strategies for the treatment of systemic lupus erythematosus (SLE) (1, 2). HCQ has been reported to reduce the risk of flare (3), the incidence of visceral involvement (4, 5), a deterioration of the renal function (6, 7), the incidence of

thromboembolic events (8, 9), the risk of infection (10), and even mortality (11, 12). Based on these observational findings, HCQ is recommended in all cases of SLE (1, 2). In Japan, however, HCQ was not widely used until 2015, when the drug was accepted as a drug with medical insurance coverage. A retrospective study including 122 cases of SLE treated with HCQ showed that the 1-year continuation rate was 79.5% (13), while adverse events (AEs) frequently occurred within two months after starting the therapy. The

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authors further showed improvements in the disease activity, anti-double-stranded DNA (anti-dsDNA) antibody titer, and CH50 over a period of 1 year in 42 cases on maintenance therapy compared with those in a control population (14). Another study including 35 cases of SLE treated with HCQ showed the beneficial effects of HCQ on the disease activity and dose of prednisolone (15). We herein present the results of an observational study on 47 cases of SLE treated with HCQ in a Japanese municipal hospital with the focus on the continuation rate and safety as well as the possible efficacy of HCQ treatment in selected cases.

Materials and Methods

Patients

All SLE patients who visited our department during the period between April 2009 and July 2019 and for whom treatment with HCQ was started were included in this study. The diagnosis of SLE was based on the American College of Rheumatology 1997 criteria (16, 17) or Systemic Lupus International Collaborating Clinics 2012 criteria (18).

Data extraction

A retrospective chart review was performed. The extracted data included the dates of initiation and discontinuation of HCQ and the last observation; AEs and their dates; doses of glucocorticoid and immunosuppressive agents 3 and 6 months prior to initiation of HCQ; SLE disease activity index (SLEDAI), anti-dsDNA IgG antibody (determined by enzyme-linked immunosorbent assay), anti-DNA antibody (determined by a radioimmunoassay), immune complex (IC; determined by C1q solid-phase enzyme immunoassay), serum complement activity (CH50), and C3 and C4 at the time of initiation of HCQ treatment. AEs were defined as any events leading to the discontinuation of HCQ or a decrease in the dose, while a decrease in the HCQ dose due to sustained remission was not regarded as AEs. To examine the efficacy of HCQ which is independent of any preceding immunosuppressive therapy, we selected cases in which the doses of glucocorticoid and immunosuppressive agents remained unchanged for at least 6 months. We therefore included patients with an initial onset of SLE for this purpose unless treatment with a glucocorticoid or immunosuppressive agent was concomitantly started. We extracted the clinical and immunological data at 3, 6, and 12 months after starting treatment with HCQ. Two of us independently extracted the data and any disagreement was resolved through consensus.

Statistical analyses

The variable data are expressed as the means (standard deviation) or medians (range) depending on their distributions. To investigate the continuation rates of HCQ, the survival rates of HCQ treatment without AEs, without a temporary discontinuation of HCQ treatment and without any per-

manent discontinuation of HCQ treatment were evaluated with Kaplan-Meier curves. For analyses of the efficacy of HCQ, the chronological changes in the data were compared by a repeated measures analysis of variance (ANOVA) or the Friedman test as appropriate. For the analyses, values that were less than the measurable range were replaced with a possible highest value (i.e., CH50<14.0 replaced with 13.9). By this imputation, we considered that any differences between the chronological data would be minimal, so that any significant differences based on these data could always suggest significant differences. Missing data were excluded from the analyses. The threshold of $p < 0.05$ was considered to be statistically significant. All analyses were conducted using the R studio software program (R version 3.6.1).

Results

Patient characteristics

Forty-seven patients were included in this study (Table 1). In 2015, we carefully considered the indications for HCQ administration in selected cases of SLE, but gradually began to consider it for all the cases regardless of the disease activity. Thereafter, the period of initiation of HCQ in our patients were between May 2016 and April 2019. The median follow-up period was 102 weeks. The median dose of prednisolone was 10 mg/day, and concomitant immunosuppressive agents other than a glucocorticoid were used in 15 patients (31.9%) (azathioprine in 8 patients, mycophenolate mofetil in 3 patients, tacrolimus in 3 patients and methotrexate in 1 patient).

Continuation rate

AEs occurred in 25 patients (53.2%). In 4 of those patients, treatment with HCQ could be continued at a decreased dose. In the remaining 21 patients, HCQ treatment was stopped, but readministration of the drug was tried in 17 patients. Treatment with HCQ could be continued in 11 (64.7%) of the 17 patients. Therefore, HCQ treatment could be continued in 15 (60.0%) of the 25 patients who experienced AEs. The continuation rate of HCQ for a period of 1 year was 78.3% (36 of 46 patients; one case was lost to follow up at month 10 while taking HCQ). The Kaplan-Meier curves for AE-free survival, discontinuation-free survival, and survival without permanent discontinuation during the follow-up period are shown in Fig. 1. As illustrated in these survival curves, by trying to reduce the dose (but not discontinue HCQ) in the case of mild AEs, the survival probability of HCQ treatment is expected to improve from (A) to (D). Furthermore, by trying to readminister the drug in the cases that stopped HCQ, it would then improve from (D) to (P).

Adverse events

Twenty-six AEs occurred in 25 patients (53.2% of the to-

Table 1. Patient Characteristics.

Male/female ratio	5/42
Age (mean±SD)	41.6±16.7
Duration between diagnosis to HCQ (day) (median, range)	608 (0, 11,942)
Follow-up period (day) (median, range)	717 (197, 1,225)
Prednisolone dose (mg) (median, range)	10 (0, 50)
Use of immunosuppressives n, (%)	15 (31.9%)
SLEDAI (median, range)	6 (0, 31)

SD: standard deviation, HCQ: hydroxychloroquine, SLEDAI: systemic lupus erythematosus disease activity index

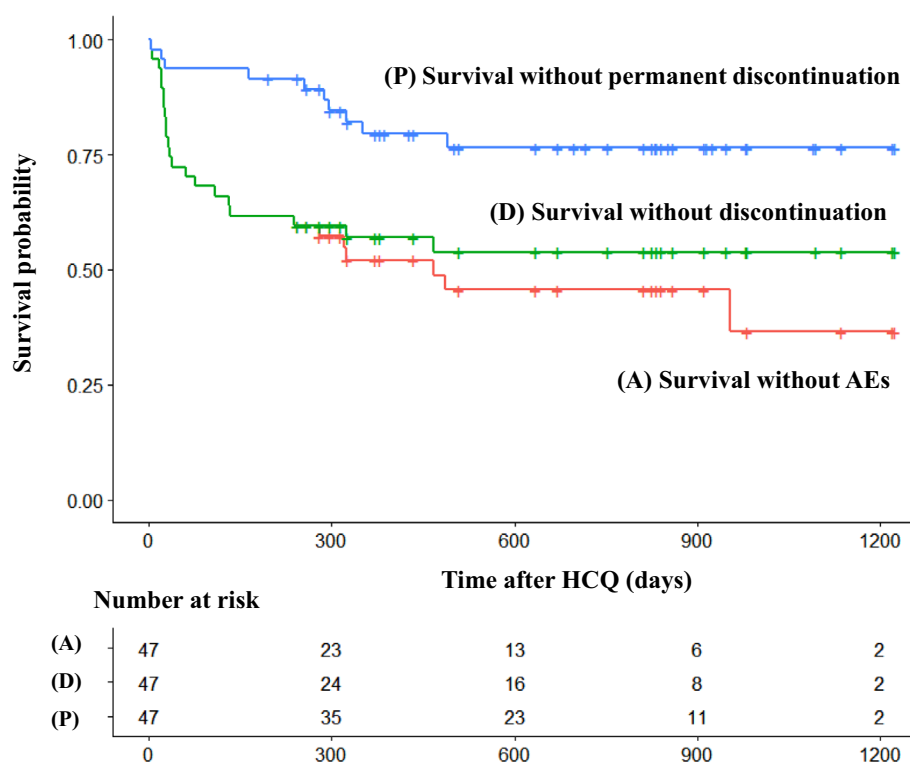


Figure 1. Survival probabilities without AEs, temporary discontinuation and permanent discontinuation. The curves for A, D and P mean AE-free survival, temporary discontinuation-free survival, and permanent discontinuation-free survival. Estimated proportions of the cases with ‘AEs’, the cases with a ‘discontinuation’ of HCQ, and the cases with a ‘permanent discontinuation’ are illustrated as 1.00-(A), 1.00-(D), and 1.00-(P), respectively. AEs: adverse events, HCQ: hydroxychloroquine

tal cases) (Table 2). There were three types of AEs: the development of cutaneous lesions, gastrointestinal symptoms, and other AEs. The development of cutaneous lesions was the most common AE (25.5%), while cutaneous lesions in two patients were subsequently considered to have been caused by lupus or another drug. The median time to the development of cutaneous lesions was 26.5 days (range, 4-954 days) and the time was <6 weeks in 10 patients (83.3%). We suggested the readministration of HCQ or a decrease in the dose to all of the 12 patients with cutaneous lesions, and 10 patients accepted it. Two of them had urticaria or itching and could continue HCQ treatment at lower doses without discontinuation. HCQ treatment was discontinued but restarted at a lower dose in 4 patients. HCQ treatment could

be subsequently continued in all of them, while the dose of HCQ could be even returned to the original dose in 3 of those patients. The remaining 4 patients received a desensitization regimen (19), which was successful in 2 patients (50%); one of the two patients with failure had a recurrence of rash and the other refused to continue HCQ treatment during the regimen. Accordingly, the continuation rate for the cases with cutaneous AEs was 66.7% (8/12).

Four patients (8.5%) had gastrointestinal symptoms including 3 patients with diarrhea and 1 patient with epigastralgia and loose stools. The median time to gastrointestinal AEs was 353 days (133-486 days). All of them received the readministration of HCQ or a decrease in the dose, but 2 of them could not continue HCQ treatment due to recurrence.

Table 2. Adverse Events: Reasons for Discontinuation of HCQ or Decrease of Dose.

	Frequency of AEs	Frequency of AEs causing permanent discontinuation
Cutaneous lesions	12 (25.5%)	4 (8.5%)
rash	11 (23.4%)	4 (8.5%)
itching	1 (2.1%)	0 (0%)
Gastrointestinal symptoms	4 (8.5%)	2 (4.3%)
Diarrhea	3 (6.4%)	2 (4.3%)
Epigastralgia & loose stool	1 (2.1%)	0 (0%)
Miscellaneous	10 (21.3%)	4 (8.5%)
breast feeding	2 (4.3%)	2 (4.3%)
patient's reasons*	2 (4.3%)	0 (0%)
hypoglycemia	1 (2.1%)	1 (2.1%)
visual disturbance	1 (2.1%)	0 (0%)
fever	1 (2.1%)	1 (2.1%)
thrombocytopenia	1 (2.1%)	0 (0%)
chorea	1 (2.1%)	0 (0%)
alopecia	1 (2.1%)	0 (0%)

*patient's reasons included 1) temporal discontinuation due to forgetfulness of the regular visit in one patient and 2) decrease of the dose due to patient's concern on high cost of the drug in another.

HCQ: hydroxychloroquine, AEs: adverse events

Table 3. Changes of Clinical and Laboratory Data during 12 Months after HCQ Treatment.

	M0	M3	M6	M12	p value
PSL, median (range)	5 (0-10)	5 (0-10)	5 (0-15)	4 (0-8)	<0.05
SLEDAI, median (range)	5 (0-12)	4 (0-7)	3.5 (0-7)	2 (0-8)	<0.01
α DNA (IU/mL)*, median (range)	13 (<2.0-100)	8.5 (<2.0-61)	5.1 (<2.0-51)	4.6 (<2.0-60)	<0.001*
α dsDNA (IU/mL)*, median (range)	18.5 (<10-113)	14 (<10-46)	14 (<10-47)	21 (<10-45)	N.S.*
IC (μ g/mL)*, median (range)	<1.5 (<1.5-8.7)	<1.5 (<1.5-5.5)	<1.5 (<1.5-6.2)	<1.5 (<1.5-4.5)	<0.05
C3 (mg/dL), median (range)	70 (42-121)	74 (44-115)	70.5 (45-139.5)	72 (53-133)	N.S.
C4 (mg/dL), mean (SD)	12.4 (\pm 6.7)	12.3 (\pm 5.8)	12.7 (\pm 5.7)	13.0 (\pm 4.8)	N.S.
CH50 (/mL), mean (SD)	31.6 (\pm 9.6)	34.2 (\pm 7.9)	35.3 (\pm 9.3)	37.1 (\pm 9.7)	<0.05*

* For the analyses, the data less than measurable range (α DNA<2.0, α dsDNA<10, IC<1.5, and CH50<14.0) were replaced with a possible highest value (1.9, 9, 13.9, and 1.4, respectively)

M: month, PSL: prednisolone, SLEDAI: systemic lupus erythematosus disease activity index, α DNA: anti-DNA antibody on the radioimmunoassay, α dsDNA: anti-dsDNA antibody on the ELISA, N.S.: not significant, IC: immune complex, SD: standard deviation, CH50: serum complement activity

The continuation rate for the cases with gastrointestinal AEs was 50.0% (2/4).

Among the other AEs, hypoglycemia repeatedly occurred in one patient during HCQ therapy, leading to the discontinuation of the treatment. HCQ treatment was discontinued in one patient who complained of decreased vision, but the treatment could be continued after obtaining normal results on ophthalmologic examinations. HCQ treatment that was started in two patients during pregnancy was stopped for breast feeding according to the instructions on the drug package insert. There were several events leading to either the discontinuation of treatment or a decrease in the dose that were not related to HCQ itself: the patient's reasons (i.e., forgetfulness of regular visit), chorea (probably due to a hyperglycemic state), fever and thrombocytopenia (The

last two were subsequently thought to be caused by lupus itself).

Efficacy in cases on stable treatment

In the 16 cases in which the doses of glucocorticoid and immunosuppressive agents remained unchanged for at least 6 months prior to initiation of HCQ treatment (Supplementary material), the changes in the prednisolone dose, SLEDAI, anti-DNA antibody titer, and the levels of immune complex and CH50 were significantly different between month 0 and month 12 after the start of HCQ treatment (Table 3). Among the parameters tested, the changes of CH50 and C4 were evaluated with repeated measures ANOVA, showing a gradual improvement in the mean levels of CH50 within 12 months after starting HCQ (Fig. 2). Fortunately,

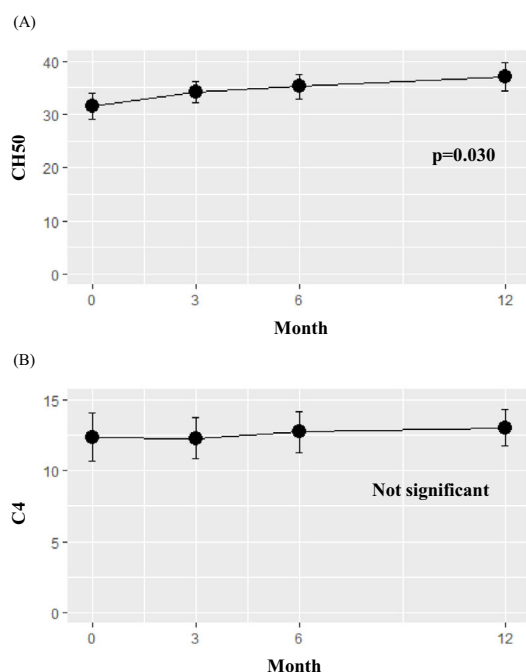


Figure 2. Changes in the average levels of C4 and CH50 for one year. The error bar expresses the standard error.

the doses of immunosuppressive agents were unchanged for the 12 months in those cases except for one case in which concomitant treatment with azathioprine was discontinued, suggesting an effect of HCQ independent of other concomitant immunosuppressive therapy. HCQ treatment could be continued for 1 year in 14 of the 16 patients. One of the 16 patients was lost to follow-up at month 10 and the other patient stopped taking the drug due to hypoglycemia at month 6.

Discussion

In our study population with SLE, the continuation rate of HCQ treatment for 1 year was 78.3% and more than half of the patients had AEs. However, by recommending drug re-administration, a large proportion (64.7%) of the patients who stopped HCQ treatment could continue the treatment. As illustrated in Fig. 1, our results suggested the importance of trying to readminister HCQ or decrease the dose even after the occurrence of AEs. The results of an analysis of the efficacy of HCQ treatment only in cases with stable treatment showed significant differences in SLEDAI, anti-DNA antibody, IC and CH50 over a period of 1 year as the pure effects of HCQ, which would likely lead to a significant decrease in the prednisolone dose.

A retrospective cohort study showed that the continuation rate of HCQ treatment in a Japanese population with SLE was 79.5% (13), which is very close to that in our study. Among the AEs that led to the permanent discontinuation of HCQ treatment, rash and gastrointestinal symptoms were frequent in that study [6/122 (4.9%) and 5/122 (4.1%), respectively]. Similarly, the frequencies of cutaneous and gas-

trointestinal AEs leading to a permanent discontinuation were 8.5% and 4.3% in our study (Table 2). When we investigated any AEs that occurred during the follow-up period, the two most frequent AEs were also rash and gastrointestinal symptoms but with higher frequencies of 25.5% and 8.5%, respectively. By readministering HCQ including a desensitization strategy, a large proportion (64.7%, 11/17) of the patients could continue treatment with the drug. Several strategies for desensitization have been reported (19, 20). A regimen of a gradual increase from 0.1 mg to 200 mg was successful in all 4 cases in one study (19), although our success rate for this regimen was low (50%). Recently, a simpler dose-escalation regimen for cutaneous lesions due to HCQ, beginning at 40 mg/day with weekly increments of 40 mg to 200 mg/day, was successful in 13 of 14 cases (92.9%) (20). The results of those studies suggest that either the readministration or desensitization of HCQ should be tried in many cases in which HCQ treatment was discontinued due to AEs.

Miyagawa et al. investigated the efficacy of HCQ treatment for SLE patients during maintenance therapy, and they reported significant improvements of SLEDAI, anti-dsDNA antibody titer, CH50 and glucocorticoid dose in patients treated with HCQ (14). Their definition of “maintenance therapy” was treatment with a glucocorticoid at a dose of less than 0.3 mg/kg regardless of previous treatment with a high-dose glucocorticoid or concomitant treatment with immunosuppressants. However, any changes in such immunosuppressive therapies just prior to or during the study period may have affected clinical and immunological improvements. On the other hand, we examined the efficacy of HCQ treatment in only 16 cases in which immunosuppressive therapies prior to HCQ administration remained unchanged for at least six months. Fortunately, the doses of concomitant immunosuppressive drugs (other than HCQ or a glucocorticoid) remained unchanged (or decreased in one case) for one year after the initiation of HCQ treatment. As a result, SLEDAI, CH50, and the dose of prednisolone significantly improved during a period of 1 year. By imputation for values less than the measurable range, the changes of IC or anti-DNA antibody (RIA) could also be estimated, which resulted in significant differences. From these findings, HCQ treatment improved clinical and immunological data, independently of concomitant immunosuppressive therapy, which would likely lead to a significant decrease in the prednisolone dose.

There are several limitations associated with this study. First, the study was retrospective in nature and included a small sample size, thus leading to some potential selection bias. Second, the duration of preceding immunosuppressive therapies that may have affected the immunological data for analysis of efficacy is unclear. Third, our population included several patients for whom clinical data were missing, as was often the case in similar studies. Despite these limitations, we believe that the results based on real-world data from a municipal hospital may be useful in the clinical set-

ting of HCQ use in Japan. In conclusion, our cohort study of SLE in a Japanese municipal hospital showed a high continuation rate of HCQ treatment. Although more than half of the patients had AEs, either the readministration or a decrease in the drug dose was successful in many cases and should be considered in such cases. For cases with stable treatment for at least six months, significant improvements in clinical and immunological data were observed for one year with HCQ added to the stable therapy.

The authors state that they have no Conflict of Interest (COI).

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