Combining maintenance therapy with hydroxychloroquine increases LLDAS achievement rates in individuals with stable systemic lupus erythematosus

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Summary

Background: Hydroxychloroquine (HCQ) has been positioned as an anchor drug for systemic lupus erythematosus (SLE). There is evidence supporting the benefits of HCQ; however, the effect of additional HCQ in maintenance therapy remains unclear.

Methods: Thirty patients with SLE who visited Juntendo University Hospital were receiving maintenance therapy before HCQ treatment and were able to complete more than 104 weeks of HCQ treatment were analyzed. Anti-DNA antibody titers, IgG and CH50 levels, the maintenance dose of corticosteroids, the SLE disease activity index (SLEDAI), and the achievement of the Lupus Low Disease Activity State (LLDAS) were evaluated at baseline and at 12, 24, 52, and 104 weeks after HCQ initiation.

Results: We observed improvements in the anti-DNA antibody titers, IgG and CH50 levels, maintenance dose of corticosteroids, and SLEDAI at week 104 relative to baseline. Moreover, the LLDAS achievement rate increased over time from 10% at baseline to 43% and 80% at week 52 and week 104, respectively.

Conclusion: Two years of continuous HCQ treatment led to improvements in SLE disease activity and corticosteroid dose and an increase in LLDAS achievement, thereby demonstrating the significance of the maintenance dose of HCQ for the management of SLE.
Introduction

Although the 10-year survival rate of systemic lupus erythematosus (SLE) has improved to nearly 90%, organ damage associated with this long-term disease remains a problem. The causes of organ damage are largely classified into two groups: damage due to the disease itself and damage from drug-related adverse events. Early-stage organ damage is caused by disease activity, while late-stage damage is caused by drug-related adverse events, particularly due to corticosteroid use. The hazard ratio for organ damage risk per 1 mg of prednisolone (PSL) conversion is 1.054. The International Treat-to-Target SLE Working Group has established remission and low disease activity as the therapeutic target; by regarding relapse prevention as a realistic target, they recommend reducing the glucocorticoid dose as low as possible or discontinuing its use while continuing immunosuppressive maintenance therapy.

Hydroxychloroquine (HCQ) has been positioned as an anchor drug for achieving this target, and according to the European League Against Rheumatism (EULAR) recommendations updated in 2019, all patients with SLE should be treated with a dose not exceeding 5 mg/kg ideal body weight. Evidence supports the benefits of using HCQ for SLE treatment. Moreover, HCQ has been used as a mainstay in the treatment of SLE worldwide. Clinical studies and cohorts outside Japan have reported varied rates of antimalarial drug use, including HCQ, ranging from 50% to 80%; nevertheless, such drugs were
used in most cases, and administration was initiated at the time of diagnosis.\textsuperscript{7,10,13} In
Japan, the use of HCQ for SLE was not permitted initially due to concerns over
chloroquine retinopathy; however, HCQ for SLE was approved in 2015. As a result, the
maintenance dose of corticosteroids was relatively high in this study. Moreover,
corticosteroid-related organ damage remains an issue. HCQ therapy had been withheld
from many patients because of a lack of evidence regarding its use during the stable
phase of SLE. Additionally, in other countries where HCQ approval was also delayed or
in cases of delayed consultation with specialists, HCQ therapy was withheld.

The achievement of Lupus Low Disease Activity State (LLDAS) can be regarded as
an important indicator of the therapeutic effect of HCQ. It has been reported that
achieving LLDAS suppresses disease flare, consequently suppressing the rise in the
Systemic Lupus International Collaborating Clinics Damage Index (SDI)\textsuperscript{14} and
improving health-related quality of life.\textsuperscript{15}

Accordingly, we evaluated the effect of adding HCQ to the maintenance therapy of
patients with SLE and investigated whether the corticosteroid dose could be reduced or
maintained during the stable phase. Moreover, we analyzed disease activity leading to
the achievement of LLDAS. Finally, we examined how well the patients achieved or did
not achieve LLDAS over the clinical course.
**Materials and Methods**

Of the 67 patients with SLE who visited the department that initiated HCQ treatment between January 2015 and March 2017, 30 who were receiving maintenance therapy at the start of HCQ treatment and were able to complete at least 104 weeks of HCQ treatment were analyzed. Considering the disease specificity of SLE, we set the follow-up period in this study to 104 weeks; this would enable the evaluation of the continuation rate and the reason for discontinuation after the introduction of HCQ in the 67 patients, thus permitting the assessment of the safety of HCQ.

HCQ dose was based on ideal body weight (calculated using the modified Broca formula) as follows: 200 mg/day for an ideal body weight <46 kg; 200 mg and 400 mg on alternate days for a weight $\geq$46 kg and <62 kg; and 400 mg/day for a weight $\geq$62 kg. Lower doses were tolerated depending on the judgment of the attending physician and the side effects.

The diagnosis of SLE was based on the American College of Rheumatology Revised Criteria (1997).

Maintenance therapy was defined as the fixed use of the same type and dose of corticosteroids or immunosuppressants for 3 months or longer. We evaluated the SLE disease activity index 2000 (SLEDAI-2K), anti-DNA antibody titer, IgG level, CH50 level, the maintenance dose of corticosteroids (PSL conversion), and LLDAS at the start of HCQ treatment as well as at 12, 24, 52, and 104 weeks after the start of HCQ.
treatment. Flare was defined as “severe flare,” as described in the Safety of Estrogen in Lupus National Assessment-SLEDAI.\textsuperscript{18}

We used SPSS Statistics version 23 (IBM Corp., Armonk, NY, USA). The Wilcoxon signed-rank test was used to analyze and compare the results between the start of HCQ treatment (baseline) and those at 12, 24, 52, and 104 weeks after treatment initiation. A P-value <0.0125, as determined by the Bonferroni method, was regarded as statistically significant. We used the Mann-Whitney U test to analyze and compare the baseline data of the LLDAS-achieved and non-achieved cases. We used the McNemar test to analyze and compare the LLDAS achievement rate between low-dose and normal-dose cases.

This study was approved by the ethical committee of Juntendo University Hospital (No. 19-152). Informed consent was obtained in the form of opt-out on the hospital’s website (https://www.gcprec.juntendo.ac.jp/kenkyu/).

**Results**

Of the 67 patients, 13 discontinued HCQ treatment due to side effects, the most common of which were ophthalmological symptoms in three patients, followed by headaches, gastrointestinal symptoms, and skin symptoms in two patients each. After ophthalmological examinations, we confirmed that none of the patients with ophthalmological symptoms had HCQ retinopathy. Another 24 patients had an observation period of fewer than 104 weeks. Therefore, we analyzed 30 patients in this
Tables 1 and 2 show the baseline data from the start of HCQ treatment. The mean age of the patients was 37.4±9.9 years, and the mean number of disease years was 13.4±9.9 years. The SLEDAI was 5.4±3.1, anti-DNA antibody titer was 23.0±35.6 IU/mL, CH50 level was 32.3±9.9 mg/dL, IgG level was 1526±499 mg/dL, and the LLDAS achievement rate was 10%.

Table 1 also describes the treatments at the time of HCQ initiation. The mean corticosteroid dose was 10.2±3.9 mg/day. Immunosuppressants were being used by 18 patients (60%), including tacrolimus in 8 patients (60%), mycophenolate mofetil (MMF) in 1 patient (3%), azathioprine in 6 patients (20%), and mizoribine (MZB) in 6 patients (20%). Mizoribine is a type of immunosuppressant and a purine antimetabolite, which inhibits lymphocyte proliferation and the production of antibodies. It was originally marketed in Japan in 1986 and was indicated for lupus nephritis in 1990. It was developed in Japan and marketed earlier than other immunosuppressants. Therefore, it is relatively widely used in Japan; however, it is similarly used in South Korea and China. Notably, no patients used methotrexate.

Figure 1 shows the trends in anti-DNA antibody titers, CH50 levels, SLEDAI, corticosteroid dose, and LLDAS at 12, 24, 52, and 104 weeks after HCQ initiation. Relative to baseline, significant differences ($P < 0.0125$) were observed for anti-DNA antibody titers after week 52, for IgG levels after week 24, for CH50 levels at week 104,
for the SLEDAI after week 24, and for the corticosteroid dose after week 12. From baseline to week 52 and 104, the mean SLEDAI decreased from 5.4±3.1 to 3.1±3.0 and 2.0±1.7, respectively, and the mean anti-DNA antibody titer decreased from 23±35.6 to 12.9±19.3 and 9.8±17.6 IU/mL, respectively; the mean IgG level decreased from 1526±499.8 to 1379±428.2 and 1361±344.7 mg/dL, respectively; mean CH50 level increased from 32.3±9.9 to 32.4±9.43 and 35.0±9.3 mg/dL, respectively; and mean corticosteroid dose decreased from 10.0±3.9 to 8.1±3.9 and 6.4±2.6 mg/day, respectively.

Figure 2 shows the LLDAS achievement rates. Only three patients (10%) had achieved LLDAS at baseline; this increased to 13 patients (43%) at week 52 and 24 patients (80%) at week 104. To investigate whether the patients who did not achieve LLDAS by week 104 would have achieved LLDAS after a longer treatment period, if they were resistant, or if their corticosteroid dose was not reduced by their physician despite their condition being stable, we additionally analyzed LLDAS non-achievement.

Figure 3 shows the trends in parameters for LLDAS-non-achieved patients at week 104. We used the Mann-Whitney U test to analyze and compare the baseline data of LLDAS-achieved and -non-achieved cases. Anti-DNA antibody titers, CH50 and IgG levels, the corticosteroid dose, and the SLEDAI values were not significantly different between the two groups. Although there were no significant differences between baseline and post-treatment, the mean anti-DNA antibody titer decreased from
42.9±47.2 to 18.5±17.4 IU/mL, mean CH50 level increased from 24.6±14.8 to 26.4±12.4 mg/dL, mean SLEDAI decreased from 7.6±2.3 to 3.8±2.2, and mean corticosteroid dose decreased from 11.5±4.9 to 10.5±2.2 mg/day for these patients.

Three patients met the criteria of the flare. One patient had SLE retinopathy, one patient changed medication from MZB to MMF due to residual arthritis, and one patient changed medication from MZB to MMF due to residual proteinuria.

Discussion

In this study, we showed that HCQ treatment resulted in a significant reduction in the corticosteroid dose even during the maintenance period. Moreover, the risk of harm from long-term corticosteroid use was reduced with HCQ treatment. Our study, therefore, demonstrated a strategy for the discontinuation of corticosteroids in SLE management.

We analyzed patients with stable SLE who received additional HCQ. The patients exhibited generally favorable clinical progression, a decreased SLEDAI, a reduction in the corticosteroid dose, and an increase in LLDAS achievement. Severe relapse was observed in only one patient who immediately went into remission; then, over the course of 2 years, there was no mild or moderate relapse. Hence, relapse was prevented during that time.

LLDAS, as a realistic therapeutic target of the EULAR recommendations updated in
2019, is used to define low disease activity, and increasing the achievement rate of LLDAS is of great clinical significance. At week 104 of added HCQ treatment, six patients did not achieve LLDAS. In all six, the corticosteroid dose was not achieved below 7.5 mg (Table 3), and we surmised that the main cause of LLDAS non-achievement was the high corticosteroid dose.

Furthermore, despite there being no statistically significant difference, the mean baseline anti-DNA antibody titer of LLDAS-non-achieved patients (42.9 IU/mL) was higher than that of the LLDAS-achieved patients (18.5 IU/mL), which is considered to be the cause of the difficulty in reducing the corticosteroid dose. We thought that sustained immunoserologic activity, such as high anti-DNA antibody titers and hypocomplementemia, may have made the attending physician or the patient reluctant to reduce the corticosteroid dose.

In one patient, the corticosteroid dose was increased due to arthritis deterioration; however, a chlamydia infection was later discovered, and reactive arthritis was thought to be more likely than SLE arthritis. In another patient, the corticosteroid dose was increased due to a fever, despite the conditions not fitting the definition of a relapse. We also observed that patients who had previously experienced relapse and those with high anti-DNA antibody titers had their corticosteroid dose decreased slowly.

Over the 2-year observation period, 83% of the patients had reduced corticosteroid doses, 13% continued on the same dose, and only one patient (3%) had an increased
dose. Even among the LLDAS-non-achieved patients, some had decreased anti-DNA antibody titers and corticosteroid dose reductions, and LLDAS achievement was plausible beyond a clinical course of 2 years. In some patients, corticosteroid use could have been reduced even further or discontinued altogether.

Chloroquine retinopathy was previously reported in Japanese patients who had used chloroquine for nephritis, among other conditions, and the sale of this drug was discontinued in Japan in 1974.\textsuperscript{19, 20} HCQ is widely used outside Japan as a treatment for SLE; however, it was only approved in Japan in 2015. At our hospital, we perform ophthalmological examinations every 6 to 12 months for the early detection of HCQ retinopathy\textsuperscript{21}; however, none of the patients presented with HCQ retinopathy at the very early stages.

Although the 30 patients analyzed in the present study were able to continue HCQ treatment for 2 years due to a lack of serious side effects, some patients presented with mild gastrointestinal symptoms, such as diarrhea, during the relatively early stages after treatment initiation (within 1 month). However, these were relatively minor issues that resolved spontaneously.

Among the 67 patients who underwent not only maintenance therapy but also additional HCQ treatment, a total of 13 patients (19\%) discontinued treatment due to symptoms that may have been side effects. The three patients who experienced ophthalmological symptoms included a patient with myodesopsia, one with vision...
deterioration, and one with visual field defects suspected to be related to macular edema, central serous chorioretinopathy, and glaucoma. Although none of the patients were considered to have HCQ retinopathy by the ophthalmologist, they all discontinued HCQ treatment at the discretion of the attending physician.

According to Yokogawa et al., 12 approximately 7.8% of Japanese patients discontinue HCQ treatment. A systematic review by Ruiz-Irastorza et al. 22 suggested that 15% of patients were unable to continue SLE treatment using antimalarial drugs, including chloroquine, due to side effects. Based on these observations, we believe that Japanese patients can expect a similar level of tolerability to HCQ treatment as European and American patients.

In 11 of the 30 patients, the HCQ dose was lower than the originally prescribed dose due to the physician's judgment or side effects. Among LLDAS-achieved patients, 8 out of 24 patients received low doses of HCQ, and 3 out of 6 LLDAS-non-achieved patients received low doses. We used the McNemar test to analyze and compare the LLDAS achievement rate between low-dose and normal-dose cases. There was no significant difference in the rate of LLDAS attainment between the two groups, suggesting that low doses may be sufficient. We plan to increase the number of patients for future research.

Five of the 67 patients who were administered HCQ during maintenance therapy eventually discontinued this treatment. The reasons for this included abdominal symptoms, pruritus, malaise, arthritis, and central serous chorioretinopathy. The
maximum, minimum, and mean time to discontinuation were 7 months, 7 weeks, and 3.4 months, respectively. When the clinical course of these cases at 104 weeks after treatment initiation was compared with that of 30 cases that continued HCQ usage, only one case from the former group achieved LLDAS after the additional belimumab administration, whereas LLDAS was achieved in 24 patients in the latter group.

This study was limited by its single-center, retrospective, observational design, relatively short observation period, and small sample size. Confirmation of our findings will require a multicenter prospective study and comparative analysis.

In conclusion, this was the first study that examined the effect of HCQ in stable-phase SLE patients from a perspective that included LLDAS and thereby demonstrated the usefulness of adding HCQ to maintenance therapy for SLE. Over 2 years of observation with additional HCQ, there were improvements in the SLE disease activity index, a reduction in the corticosteroid dose, and an increase in the LLDAS achievement rate from 10% to 80%. Moreover, we demonstrated the possibility of increasing the achievement rate by further extending the observation period. Thus, HCQ may be useful as a mainstay drug for SLE therapy in Japanese patients. Due to racial differences, we believe that it is important for patients to undergo periodical ophthalmic examinations for HCQ retinopathy, and studies involving a larger number of patients should be performed.
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Declaration of Conflicting Interests

The authors declare that there is no conflict of interest.


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**Table 1.** Baseline characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>30</td>
</tr>
<tr>
<td>Age (y)</td>
<td>37.4±9.9</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>28 (93%)</td>
</tr>
<tr>
<td>Disease duration (y)</td>
<td>13.4±9.9</td>
</tr>
<tr>
<td>Anti-DNA Ab (IU/mL)</td>
<td>23.0±35.6</td>
</tr>
<tr>
<td>CH50 (U/mL)</td>
<td>32.3±9.9</td>
</tr>
<tr>
<td>IgG (mg/dL)</td>
<td>1526±499</td>
</tr>
<tr>
<td>SLEDAI (point)</td>
<td>5.4±3.1</td>
</tr>
<tr>
<td>LLDAS, n (%)</td>
<td>3 (10%)</td>
</tr>
</tbody>
</table>

**Initial hydroxychloroquine treatment**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid dose (PSL mg/day)</td>
<td>10.2±3.9</td>
</tr>
<tr>
<td>Immunosuppressants, n (%)</td>
<td>18 (60%)</td>
</tr>
<tr>
<td>TAC, n (%)</td>
<td>8 (26%)</td>
</tr>
<tr>
<td>MMF, n (%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>AZP, n (%)</td>
<td>6 (20%)</td>
</tr>
<tr>
<td>MZB, n (%)</td>
<td>6 (20%)</td>
</tr>
<tr>
<td>MTX, n (%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

**Antibody profile at the start of hydroxychloroquine treatment**
<table>
<thead>
<tr>
<th>Antibody Type</th>
<th>Positive Cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-DNA Ab, n (%)</td>
<td>14/30</td>
<td>46%</td>
</tr>
<tr>
<td>Anti-U1-RNP Ab, n (%)</td>
<td>5/29</td>
<td>17%</td>
</tr>
<tr>
<td>Anti-Sm Ab, n (%)</td>
<td>2/29</td>
<td>6%</td>
</tr>
<tr>
<td>Anti-SS-A Ab, n (%)</td>
<td>6/30</td>
<td>20%</td>
</tr>
<tr>
<td>Anti-SS-B Ab, n (%)</td>
<td>4/27</td>
<td>14%</td>
</tr>
</tbody>
</table>

SLEDAI: systemic lupus erythematosus disease activity index; LLDAS: Lupus Low Disease Activity State; PSL: prednisolone; TAC: tacrolimus; MMF: mycophenolate mofetil; AZP: azathioprine; MZB: mizoribine; MTX: methotrexate.
Table 2. Breakdown of the SLEDAI at the start of hydroxychloroquine treatment.

<table>
<thead>
<tr>
<th>Clinical symptoms</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthritis</td>
<td>8 (26%)</td>
</tr>
<tr>
<td>Myositis</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Urinary casts</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Hematuria</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Pyuria</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Rash</td>
<td>14 (46%)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>7 (23%)</td>
</tr>
<tr>
<td>Low complement</td>
<td>10 (33%)</td>
</tr>
<tr>
<td>Increased DNA binding</td>
<td>14 (46%)</td>
</tr>
<tr>
<td>Fever</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>9 (30%)</td>
</tr>
</tbody>
</table>

SLEDAI: systemic lupus erythematosus disease activity index.
**Table 3.** Unachieved item in patients (n=6) who did not achieve LLDAS at week 104.

<table>
<thead>
<tr>
<th>Item</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLEDAI ≤4</td>
<td>1 (16%)</td>
</tr>
<tr>
<td>PGA ≤1.0</td>
<td>1 (16%)</td>
</tr>
<tr>
<td>No major organ activity</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>No new activity</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>PSL ≤7.5</td>
<td>6 (100%)</td>
</tr>
</tbody>
</table>

LLDAS: Lupus Low Disease Activity State; SLEDAI: systemic lupus erythematosus disease activity index; PGA: physician global assessment; PSL: prednisolone.
**Figure Legends**

**Figure 1.** Trends in data at the start of HCQ treatment and at 12, 24, 52, and 104 weeks after HCQ initiation (n=30). HCQ: hydroxychloroquine; SLEDAI: systemic lupus erythematosus disease activity index; PSL: prednisolone. *P<0.0125.

**Figure 2.** LLDAS achievement rate after hydroxychloroquine treatment initiation. LLDAS: Lupus Low Disease Activity State.

**Figure 3.** Trends in data at the start of HCQ and at 12, 24, 52, and 104 weeks after HCQ initiation in patients who did not achieve LLDAS at week 104. HCQ: hydroxychloroquine; SLEDAI: systemic lupus erythematosus disease activity index; LLDAS, Lupus Low Disease Activity State; PSL: prednisolone.