More Consistent Antimalarial Intake in First 5 Years of Disease Is Associated with Better Prognosis in Patients with Systemic Lupus Erythematosus

Rattapol Pakchotanon, Dafna D. Gladman, Jiandong Su, and Murray B. Urowitz

ABSTRACT. ***Objective.*** To examine whether more consistent use of antimalarial agents (AM) leads to better results in systemic lupus erythematosus (SLE).

Methods. From a longitudinal cohort study, we identified inception patients with a minimum of 5 years of followup. They were divided into 3 groups: patients who took AM > 60% of the time (group A), those who took AM < 60% of the time (group B), and those who did not receive AM (group C) during the first 5 years of followup. Outcomes included increase in Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI), flare, achieving low disease activity (LDA), adjusted mean Systemic Lupus Erythematosus Disease Activity Index 2000, cumulative doses of steroids (CMS), and AM-related retinal toxicity. Regression analysis models were constructed to identify predictors of the outcomes.

Results. There were 459 patients identified: 236 (51.4%) in group A, 88 (19.2%) in group B, and 135 (29.4%) in group C. The changes in SDI, flare event, and CMS were significantly lower in group A, which more often achieved LDA. Multivariable analysis revealed that the patients in group A had a lower risk of increasing SDI and were more likely to achieve LDA at Year 5 compared to the patients in group C. Patients taking AM had lower CMS over the 5 years of followup. There was only 1 patient with AM-related retinal toxicity in each group.

Conclusion. More consistent use of an AM over the first 5 years of SLE is associated with better outcomes. (J Rheumatol First Release November 15 2017; doi:10.3899/jrheum.170645)

Key Indexing Terms:
ANTIMALARIAL AGENT SYSTEMIC LUPUS ERYTHEMATOSUS DISEASE ACTIVITY

Antimalarial agents (AM), especially hydroxychloroquine (HCQ) and chloroquine (CQ), have demonstrated efficacy in systemic lupus erythematosus (SLE), mainly for constitutional symptoms (fever, fatigue, and weight loss) and mucocutaneous and musculoskeletal involvement[1,2]. Moreover, AM have additional beneficial effects beyond controlling disease activity. AM have been shown to maintain disease remission[2,3,4,5], prevent further damage[6,7,8], protect against thrombosis[9,10], and improve survival[9,11,12]. A systematic review performed mostly in patients with SLE found that the toxicities of AM were infrequent and mild, mainly gastrointestinal and cutaneous; cardiotoxicity was rare[13]. AM-related retinopathy in patients treated with HCQ and CQ was reported in only 0.1% and 2.5%, respectively, after a mean duration of use of more than 10 years[13]. Because of their efficacy and low toxicity, current guidelines widely recommend the use of AM for all patients with SLE throughout the course of the disease unless toxicity ensues or there are contraindications[14,15].

We aimed to examine the beneficial effect of AM treatment duration in the first 5 years of SLE on several longterm outcomes including damage accrual, flares, disease activity, steroid-sparing effect, and side effects, specifically AM-related retinopathy.

MATERIALS AND METHODS

Study population. The study was conducted at the University of Toronto Lupus Clinic, where patients have been followed prospectively since 1970 according to a standard protocol. Patients were included if they fulfilled 4

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or more of the American College of Rheumatology (ACR) classification criteria for SLE[16], or 3 of the ACR criteria plus a biopsy compatible with SLE.

Patient selection. An inception cohort of patients with SLE diagnosed within 1 year of presentation, seen between 1970 and 2015, was identified from the University of Toronto Lupus Clinic database. The inception SLE patients with at least 2 visits followed for a minimum of 5 years after the diagnosis of SLE were included in the current study. The patients were divided into 3 groups depending on the percentage of time that they took the AM during the 5 years of followup, as derived from their followup clinic visits. The duration of AM therapy was calculated based on patient-reported intake that was recorded in a standard protocol at every clinic visit. Patients who took AM > 60% of the time formed group A; patients who took AM < 60% of the time formed group B; and patients who did not receive AM formed group C. In our center, CQ was prescribed at a dose < 3.5 mg/kg per day, and HCQ at a dose < 6.5 mg/kg per day.

Ethical review and approval was obtained from the University Health Network Research Ethics Board (REB number 11-0397-AE). Informed consent was collected from all patients at enrollment.

Clinical assessment. At enrollment and at 2 to 6 monthly intervals, patients were evaluated according to a standard protocol. Demographic data included sex, ethnicity, age at diagnosis, and calendar year of diagnosis. Disease activity was assessed by the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K)[17], and damage was measured by Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI)[18]. Treatment variables included glucocorticosteroids (GCS), AM, and immunosuppressive drugs. All items necessary to complete the SLEDAI-2K and the SDI have been collected longitudinally in the protocol since its inception in 1970.

Outcome measures. Six outcomes were evaluated over 5 years: (1) organ damage was assessed yearly using the SDI; (2) flares were assessed at each visit and defined as any new clinical feature of the SLEDAI-2K since the previous assessment; (3) low disease activity (LDA) at Year 5 was defined by a clinical SLEDAI-2K score of ≤ 2, not including serology[19]; (4) adjusted mean SLEDAI-2K over 5 years, a valid measure of the disease activity over time, was measured in the first 5 years; (5) cumulative doses of GCS were calculated; and (6) AM-related retinal toxicity was confirmed by an ophthalmologist.

Statistical analyses. Descriptive statistics for baseline information and outcomes were presented by mean ± SD and n (%). Differences among groups were compared by ANOVA and chi-square tests. Univariate and multivariable regression analyses were performed to identify the effect of the duration of AM treatment on the development of the 6 outcomes, controlling for patients' demographics, disease activity, and treatment. Logistic regression models for binary outcomes, Poisson regression models corrected for overdispersion by Pearson scaling for ordinal rare outcomes, and linear regression for continuous outcomes were constructed. For linear regression models, group effects were coded as 1 variable with values 1 (no treatment), 2 (inconsistent treatment), and 3 (more consistent treatment). The variable estimates reported are OR, relative risk (RR) and regression coefficient (ß), correspondingly. The statistical software SAS (version 9.3; SAS Institute) was used for all statistical analyses, and the significance level was set at 5%.

RESULTS

Patient characteristics. A total of 777 inception patients with SLE were identified, of whom 459 with 5 years of followup were enrolled in our study. There were 236 (51.4%) in group A, 88 (19.2%) in group B, and 135 (29.4%) in group C.

Demographic and disease-related features in the 3 groups are comparable, as shown in Table 1. Most of the patients were women and of white ethnicity. Mean ± SD age at the diagnosis of SLE was 35.38 ± 13.09 years in group A, 34.42 ± 14.45 years in group B, and 36.94 ± 14.36 years in group C. The SLE duration ± SD at enrollment was 0.19 ± 0.24 years in group A, 0.24 ± 0.30 years in group B, and 0.25 ± 0.29 years in group C. At enrollment, SLEDAI-2K score (mean ± SD) was similar among the 3 groups: 9.67 ± 8.00 for group A, 10.51 ± 7.26 for group B, and 10.37 ± 9.87 for group C. However, renal–SLEDAI-2K is significantly lower in group A compared to groups B and C (p = 0.004). SDI score at enrollment was comparable between groups (mean ± SD; 0.07 ± 0.40 in group A, 0.08 ± 0.27 in group B, and 0.08 ± 0.39 in group C). At enrollment, lupus nephritis manifestations were lower in group A than groups B and C, whereas musculoskeletal manifestations were less common in group C. The use of immunosuppressive drugs and GCS was comparable in the 3 groups. The patients diagnosed in earlier decades had a significantly lower percentage of AM use compared to the patients diagnosed in later decades (data not shown). HCQ is the most used AM (71.54% in group A, and 61.11% in group B). The mean ± SD durations of antimalarial drug use over 5 years after enrollment were 4.7 ± 0.8 year in group A, and 1.4 ± 1.0 year in group B.

The 6 outcomes among the 3 groups are shown in Table 2. The change in SDI, flare events, and cumulative doses of GCS were significantly lower in group A. In addition, patients in group A more often achieved a state of LDA compared to the other groups. AM-related retinal toxicity occurred in only 1 patient in group A and 1 in group B.

In multivariable analyses, adjusting for possible confounders including sex, ethnicity, age, disease duration, disease activity (SLEDAI-2K and renal–SLEDAI-2K), and treatment (model 1 in Table 3), the patients in group A had a lower risk of increasing SDI (RR 0.71, 95% CI 0.52–0.95, p = 0.02) compared to the patients in group C, while group B was not statistically different from group C. Other variables associated with a risk of increasing SDI were the age at SLE diagnosis (RR 1.02, 95% CI 1.01–1.03, p < 0.00001) and cumulative dose of GCS (RR 1.01, 95% CI 1.01–1.02, p = 0.002). Moreover, the patients in group A were more likely to achieve LDA at Year 5 (OR 1.96, 95% CI 1.18–3.26, p = 0.009) compared to the patients in group C, while group B was not statistically different from group C. The patients taking AM more consistently had a lower cumulative dose of GCS over the 5 years of followup (ß –3.46, 95% CI –4.65 to –2.28, p < 0.0001), while group B was not statistically different from group C. There was no association between the persistence of AM intake and the number of flares (RR 0.94, 95% CI 0.82–1.09, p = 0.43) and adjusted mean SLEDAI-2K over 5 years (ß 0.10, 95% CI –0.19 to 0.40, p = 0.50). An additional analysis, in which clinical manifestations at enrollment were added as potential confounders, demonstrated that patients in group A still had a lower risk of increasing SDI, more likely achieved LDA at Year 5, and had a lower cumulative dose of GCS over the 5 years of followup compared to the patients in group C (models 2 and 3 in Table 3). Decade of entry into the clinic was not significant in any of the models.

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Table 1. Demographics and disease-related features at enrollment in the study population. Values are mean ± SD or n (%), unless otherwise specified.

Variables	Group A, AM Intake > 60% of Time, n = 236	Group B, AM Intake < 60% of Time, n = 88	Group C, Non-AM Intake, n = 135	p
Age at SLE diagnosis, yrs	35.38 ± 13.09	34.42 ± 14.45	36.94 ± 14.36	0.37
Age at enrollment, yrs	35.57 ± 13.06	34.66 ± 14.42	37.19 ± 14.34	0.36
Female	210 (89.0)	79 (89.8)	115 (85.2)	0.47
White/Black/Asian/others, %	69.1/14/5.5/11.4	67/17/6.8/9.1	76.3/11.1/8.9/3.7	0.14
SLE duration at enrollment, yrs	0.19 ± 0.24	0.24 ± 0.30	0.25 ± 0.29	0.11
Clinical manifestation at enrollment				
Lupus nephritis	38 (16.1)	27 (30.7)	49 (36.3)	< 0.001
Neuropsychiatric	34 (14.4)	21 (23.9)	27 (20.0)	0.11
Vasculitis	30 (12.7)	12 (13.6)	11 (8.1)	0.33
Mucocutaneous	132 (55.9)	46 (52.3)	76 (56.3)	0.81
Musculoskeletal	71 (30.1)	19 (21.6)	16 (11.9)	< 0.001
Serositis	33 (14.0)	9 (10.2)	14 (10.4)	0.49
Hematologic	24 (10.2)	8 (9.1)	15 (11.1)	0.89
Abnormal immunology	161 (68.2)	54 (61.4)	83 (61.5)	0.19
SLEDAI-2K score at enrollment	9.67 ± 8.00	10.51 ± 7.26	10.37 ± 9.87	0.63
Renal–SLEDAI-2K score at enrollment	1.54 ± 4.01	2.50 ± 4.26	3.02 ± 4.54	0.004
SDI score at enrollment	0.07 ± 0.40	0.08 ± 0.27	0.08 ± 0.39	0.93
Used glucocorticoids at enrollment	126 (53.4)	52 (59.1)	76 (56.3)	0.63
Used immunosuppressive drugs at enrollment	33 (14.0)	22 (25.0)	21 (15.6)	0.06

AM: antimalarial agent; SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLE: systemic lupus erythematosus; SLEDAI-2K: SLE Disease Activity Index 2000.

Table 2. Outcomes over 5 years after diagnosis of SLE in groups A, B, and C. Values are mean ± SD or n (%).

Outcomes	Group A, AM Intake > 60% of Time, n = 236	Group B, AM Intake < 60% of Time, n = 88	Group C, Non-AM intake, n = 135	p
Increase in SDI	0.61 ± 0.95	0.85 ± 1.30	1.01 ± 1.33	0.003
Flares	2.66 ± 1.96	3.16 ± 2.23	3.23 ± 2.79	0.04
LDA at yr 5	194 (82.2)	67 (76.1)	95 (70.4)	0.03
Adjusted mean SLEDAI-2K	4.36 ± 2.90	4.42 ± 2.46	4.83 ± 3.74	0.35
Cumulative doses of GCS, g	14.60 ± 11.06	20.22 ± 13.35	23.50 ± 15.04	< 0.001
AM-related retinal toxicity	1 (0.4)	1 (1.1)	0 (0)	0.45

AM: antimalarial agent; GCS: glucocorticosteroids; LDA: low disease activity; SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLE: systemic lupus erythematosus; SLEDAI-2K: SLE Disease Activity Index 2000.

DISCUSSION

The use of AM in SLE has increased over the decades. In our cohort of inception patients followed for a minimum of 5 years, we noted an increase of use from 36% in patients diagnosed prior to 1980, to 53% in those diagnosed in the 1980s, to 81% in those diagnosed in the 1990s, to 87% in those diagnosed after 2000. This increase was likely influenced by the Canadian Hydroxychloroquine Study, which showed the protective role of AM in preventing flares[3], as well as subsequent studies that demonstrated the beneficial effect of AM on thrombotic events[9,10], damage accumulation[6,7,8], and mortality[9,11,12]. Moreover, Shinjo, *et al* demonstrated a protective effect of AM on mortality among SLE patients in a time-dependent manner[12]. The study showed that mortality rates (per 1000 person-months of followup) among users receiving AM for 6–11 months, 1–2 years, and > 2 years were 3.85, 2.7, and 0.54, respectively. In our study, we have addressed the question as to whether more consistent use of AM leads to better results than patients taking AM less consistently, in an inception cohort of patients with SLE over the first 5 years of disease.

Damage in SLE was associated with a 46% increased risk of future mortality[7]. The beneficial effect of antimalarial agents on cumulative damage in inception patients with SLE has been shown in previous studies. In the Systemic Lupus International Collaborating Clinics inception cohort of 1722 patients with SLE from diverse ethnic and geographic backgrounds, Bruce, *et al* demonstrated that patients with preexisting damage taking AM had lower rates of transition to higher damage[7]. Akhavan, *et al* showed in a nested

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Table 3. Multivariable regression analyses for outcomes at 5 years (group A vs group C).

Outcomes	Statistic Types	Model 1 PE	Model 1 95% CI	Model 1 p	Model 2 PE	Model 2 95% CI	Model 2 p	Model 3 PE	Model 3 95% CI	Model 3 p
Increase in SDI	RR	0.71	0.52–0.95	0.02	0.72	0.53–0.98	0.04	0.73	0.54–0.99	0.04
Flares	RR	0.94	0.82–1.09	0.43	0.95	0.82–1.10	0.53	0.94	0.81–1.08	0.38
LDA achievement at yr 5	OR	1.96	1.18–3.26	0.009	2.09	1.25–3.52	0.005	1.88	1.11–3.19	0.02
Adjusted mean SLEDAI-2K over 5 yrs	ß	0.10	–0.19 to 0.40	0.49	0.12	–0.18 to 0.42	0.45	0.11	–0.20 to 0.42	0.49
Cumulative dose of GCS over 5 yrs	ß	–3.46	–4.65 to –2.28	< 0.0001	–3.57	–4.77 to –2.37	< 0.0001	–3.28	–4.50 to –2.06	< 0.0001

Group A: antimalarial agent intake > 60% of time; Group C: non-antimalarial agent intake. Model 1 is the primary analysis; Model 2 is the sensitivity analysis that forced musculoskeletal organ involvement into the model; Model 3 is the sensitivity analysis that forced renal organ involvement into the model. PE: parameter estimates; RR: relative risk from Poisson regression; OR from logistic regression; ß: regression coefficient from linear regression; GCS: glucocorticosteroids; LDA: low disease activity; SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000.

case-control study that the use of HCQ over the first 3 years of disease was significantly associated with less damage at 3 years after diagnosis when adjusted for disease activity and GCS dose, duration of disease, and calendar year of diagnosis (OR 0.34, 95% CI 0.13–0.87) in 481 inception patients with SLE who did not have damage at baseline[8]. Our study shows that a more consistent intake of antimalarial therapy in the first 5 years of disease is associated with a reduced rate of damage accrual.

We found that the patients taking AM more consistently had a lower cumulative dose of GCS over the 5 years of followup. This finding was noted by Meinão, *et al*, who showed that 82% of SLE patients without life-threatening manifestations taking CQ 250 mg daily could decrease prednisone by a minimum of 50% during 12 months of a randomized double-blind placebo-controlled trial, compared to 25% of patients with SLE who did not take CQ. This study also showed a significant reduction in disease exacerbations in patients using CQ[4]. Clowse, *et al* demonstrated the effect of HCQ in a prospective study of 257 pregnancies in women with SLE. In this study, they found that more women who discontinued HCQ during pregnancy took more prednisone. In addition, the average maximum daily dose of prednisone was lower among pregnant women who continued HCQ treatment than among those who did not. There was also a trend toward a lower flare rate in the HCQ treatment group compared to those who stopped taking HCQ[20]. Consistent with those previous reports, our results showed that patients who took AM more consistently more often achieved LDA at 5 years, and received a lower cumulative dose of GCS.

There are some limitations to our study. First, we calculated the duration of AM therapy based on patient-reported intake rather than by the Medication Adherence Self-report Inventory, pharmacy pill count, or antimalarial blood levels, which are more reliable measures of adherence to medication[21,22,23]. Second, our flare definition of any increase of SLEDAI-2K did not allow us to distinguish mild from severe flares. AM may have protected for severe flares. Finally, our study design was a cohort study, which might be susceptible to selection bias. According to the clinical presentation at enrollment, patients who did not take AM had more lupus nephritis and less musculoskeletal involvement. However, we demonstrated that the adjusted mean SLEDAI-2K was comparable among the 3 groups at the enrollment. Nevertheless, in multivariable analysis the consistent use of AM treatment remained an independent predictor for less damage accrual, lower cumulative steroid dose, and achieving an LDA state, even after adjusting for the adjusted mean SLEDAI-2K, renal–SLEDAI-2K, and renal and musculoskeletal involvement.

We have shown that a more consistent intake of antimalarial therapy over the first 5 years of disease (> 60% of the time) is associated with better outcomes. These findings highlight the importance of consistent intake or being prescribed AM early in the course of SLE to prevent adverse longterm outcomes.

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Correction

More Consistent Antimalarial Intake in First 5 Years of Disease Is Associated with Better Prognosis in Patients with Systemic Lupus Erythematosus

Pakchotanon R, Gladman DD, Su J, Urowitz MB. More consistent antimalarial intake in first 5 years of disease is associated with better prognosis in patients with systemic lupus erythematosus. J Rheumatol 2018;45:90-4. The second affiliation of author Rattapol Pakchotanon should be Rheumatic Disease Unit, Department of Internal Medicine, Phramongkutklao Hospital and College of Medicine, Bangkok, Thailand.

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