Long-term evaluation of antimalarials in a Dutch SLE cohort: intolerance and other reasons for non-use

M.W.P. Tsang-A-Sjoe, I.E.M. Bultink, A.E. Voskuyl

Department of Rheumatology, VU University Medical Center, Amsterdam, the Netherlands.

Abstract

Objective

Antimalarials (AMs) have been demonstrated to reduce disease activity and prevent damage accrual in SLE. Recent guidelines advise prescribing AMs in all patients with SLE. We present data from the Amsterdam Lupus Cohort on use, reasons for non-use, and dosage-related intolerance of AMs, as well as disease-related variables associated with non-use.

Methods

AM use was assessed in all our SLE patients included in a longitudinal cohort study. Demographic and disease characteristics were compared between users and non-users of AMs. Daily dosages of hydroxychloroquine (HCQ) according to lean body weight were calculated.

Results

Out of 190 SLE patients in the cohort, 139 (73.2%) were using AMs during their last visit, predominantly HCQ (136/139, 97.8%), while 92.1% (175/190) had ever used AMs. Daily dosage of HCQ was 400 mg in 115/136 (84.6%) patients. According to lean body weight, 119/136 (87.5%) had daily dosages of HCQ above the recommended 6.5 mg/kg. Patients did not use AMs (n=51) for the following reasons: intolerance (n=16), discontinued without a documented reason (n=11), never initiated (n=9), quiescent disease (n=7), contraindication (n=2), other (n=6). Only one patient discontinued HCQ due to AM-related retinopathy. Non-use of AMs was associated with a longer disease duration, higher damage accrual and a history of lupus nephritis.

Conclusion

Despite increased awareness of the importance of AM treatment in SLE, there is still room for improvement, especially in patients with lupus nephritis and/or long-standing disease. Daily dosages of hydroxychloroquine often exceeded recommendations from guidelines, but are generally well-tolerated.

Key words

systemic lupus erythematosus, antimalarials, drug dosage calculations, hydroxychloroquine, cohort studies

Michel W.P. Tsang-A-Sjoe, MD
Irene E.M. Bultink, MD, PhD
Alexandre E. Voskuyl, MD, PhD

Please address correspondence to:
Alexandre. E. Voskuyl,
Department of Rheumatology, 3A49,
VU University Medical Center,
De Boelelaan,
1081 HV Amsterdam, the Netherlands.
E-mail: AE.Voskuyl@vumc.nl

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Introduction

Over the past decade, antimalarial (AM) drugs, most notably hydroxychloroquine (HCQ), have become mainstay in the treatment of systemic lupus erythematosus (SLE) (1). Antimalarials (AMs) are recommended in almost every patient with SLE by many experts (2-5), which is in part reflected in the EULAR recommendations for the management of SLE (6) and the EULAR recommendations for the management of lupus nephritis (7). The most important beneficial effects attributed to HCQ are reduction in disease activity (8), prevention of flares (9), reduction in damage accrual (10;11), and improvement of overall survival in SLE (12). HCQ is generally well tolerated and side-effects are usually mild (4). AM related retinopathy however is a severe complication of AM use with a reported prevalence of 0.5–1% after 5 years of use (13, 14). Reported risk factors for AM related retinopathy are a daily dosage above 6.5mg/kg lean body weight and cumulative dosages over 1000 grams (15). Therefore, several guidelines have been published on the necessity of screening for AM related retinopathy (15, 16). Cardiomyopathy is another serious adverse reaction to AMs, that seems to be related to duration of use, but occurs rarely (17).

Although many authors stress the importance of AM use in SLE, these drugs are not optimally prescribed. HCQ use ranges from 55–68% in three studies from the United States (11, 18, 19) to 77% (20) in a European study. The latter study also showed that patients only treated by internists use HCQ less often than patients treated by rheumatologists only (12% *vs*. 88%). Suboptimal AM use puts patients at risk of undertreatment and identifying those patients may improve the use of AMs. To our knowledge, such data have not been published yet. Furthermore, the optimum daily dosage regarding efficacy in SLE has not yet been established. Usually, 400mg HCQ is prescribed daily unless patients have a low lean body mass, in which case 200mg is given. Costedoat-Chalumeau *et al*. showed that HCQ concentrations in whole blood might aid in optimising treatment efficacy (21), although the first report on adjusting HCQ dosage to maintain concentrations of >1000 ng/ml did not lead to a reduction in flare rate (22).

The aim of this study was to determine AM use and, in particular, to assess the reasons for non-use in our cohort. Also, clinical parameters associated with non-use were assessed. Thirdly we aimed to assess whether the dosage of AMs according to lean body weight was associated with side-effects and tolerance.

Patients and methods

Study population

The SLE cohort Amsterdam is an ongoing longitudinal study on outcome in SLE. The cohort was initiated at the VU University Medical Center (VUmc) in Amsterdam, the Netherlands, in 2007. All patients with a diagnosis of SLE, who meet four or more of the updated 1997 ACR classification criteria for SLE (23) and are at least 18 years of age are eligible for inclusion in the cohort. Subjects are recruited from the outpatient clinics of rheumatology from VUmc and Reade (formerly named Jan van Breemen Institute). VUmc is an academic center providing primary, secondary and tertiary rheumatologic care, while Reade is a rheumatologic center providing primary care for SLE patients. After enrolment, subjects have a follow-up visit every year. At each visit, data is obtained by questionnaires, semi-standardised interview, physical examination and laboratory tests. Questionnaires include the following domains: patient demographics, socio-economic status and clinical characteristics. The study was approved by the local medical ethics committee. Written informed consent is obtained from all patients before baseline visit.

Data collection

All patients included in the cohort on July 2012, were taken into our analysis. From the last visit of each subject in the cohort, the following data were obtained: age, gender, disease duration (in years), ethnicity, SLE manifestations according to the revised ACR criteria, current use of HCQ and daily dosage, HCQ use ever, use of other AMs, current prednisone use and daily dosage, current use of immunosuppressives. In addition, total number of different pre-

scriptions including AMs, body weight and length were assessed. Lean body weight was calculated using a formula developed by Janmahasatian *et al*. (24). Disease activity was measured using the 2000 modification of the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI 2k) (25). Accumulated damage was assessed with the SLICC/ACR damage index (SDI) (26).

From subjects who did not use AMs at their last visit, the following data were obtained from their medical records: reported reasons for withdrawal or not prescribing AMs, duration of past AM use and reported side-effects due to AMs. Where possible, treating physicians at the time of withdrawal were interviewed on the reason of withdrawal.

Ophthalmologic screening

In all AM users, we checked whether an ophthalmologic screening for AM related retinopathy in the past 2 years was done in order to identify any possible ascertainment bias regarding retinal toxicity.

Statistical analyses

Our data was analysed using SPSS Statistics, version 20.0 (SPSS, Chicago, IL, USA). Student *t*-test, Mann-Whitney U-test, and Chi-squared test were used where appropriate. To assess which risk factors were independently associated with non-use of AMs, a logistic regression analysis was performed with clinical parameters with $p<0.05$ in univariate analysis. A *p*-value lower than 0.05 was considered significant.

Results

Table I describes the demographic features and patient characteristics by AM drug use in all 190 patients included in our cohort. Patients were predominantly female and Caucasian. In total 73.2% (139/190) of patients were taking AMs at their last visit, of whom 97.8% (136/139) used HCQ and 2.2% (3/139) used CQ. However, 92.1% (175/190) had ever used HCQ and 4.2% (8/190) had ever used CQ. Use of other AM agents was not reported.

Dosage

The majority of patients used 400 mg HCQ as their daily dosage (115/136, 84.6%). Other reported dosages were: 200mg (18/136, 13.2%), 300 mg (1/136, 0.7%) and 600 mg (2/136, 1.5%). Daily dosage for CQ was 100 mg in all 3 patients. According to body weight 28.7% (39/136) had a daily dosage of HCQ above 6.5mg/kg. When adjusted for lean body weight 87.5% (119/136) had a daily dosage above 6.5 mg/kg, with a mean dosage of 8.81 mg/kg.

Table I. Demographic and disease characteristics and medication variables in 190 systemic lupus erythematosus patients using or not using antimalarials.

Baseline characteristics	Antimalarial use (n=139)	No antimalarial use (n=51)	*p*-value
Demographic characteristics			
Female, n (%)	126 (90.6)	45 (88.2)	0.623
Age, median (range), in years	43 (20-79)	45 (24-81)	0.326
Ethnicity:			
Caucasian, n (%)	91 (65.5)	37 (72.5)	
Asian, n(%)	8 (5.8)	4 (7.8)	
African, n (%)	13 (9.4)	4 (7.8)	
Mediterranean, n (%)	13 (9.4)	3 (5.9)	
Other, n (%)	14 (10.1)	3 (5.9)	
Length, mean ± SD (in m)	1.68 ± SD 0.092	1.68 ± SD 0.079	0.763
Weight, mean ± SD (in kg)	70.1 ± SD 15.7	72.0 ± SD 17.8	0.729
Disease characteristics			
Age at diagnosis, median (range), in years	32 (6-74)	30 (13-71)	0.798
Disease duration, median (range), in years	10 (2-37)	13 (2-35)	0.004‡
SLEDAI, mean ± SD	3.0 ± 3.37	2.9 ± 4.36	0.410
SDI, mean ± SD	1.2 ± 1.87	2.4 ± 2.57	<0.001‡
Medication			
Current HCQ use, n (%)	136 (97.8)	NA	
HCQ use ever, n (%)	139 (100)	36 (70.6)	
Current CQ use, n (%)	3 (2.2)	NA	
CQ use ever, n (%)	7 (5.0)	1 (2.0)	
Prednisone use, n (%)	61 (43.9)	29 (56.8)	0.208
Prednisone dose, mean (in mg/day)	5.16	5.11	0.498
Immunosuppressives, n (%)	56 (40.3)	25 (49.0)	0.455
Number of different prescriptions, mean ± SD	5.4 ± SD 2.7	5.7 ± SD 3.4	0.617

SD: standard deviation; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SDI: Systemic Lupus International Collaborative Clinics Damage Index; HCQ: hydroxychloroquine; CQ: chloroquine; NA: not applicable. ‡Significant values.

Ophthalmologic screening

Screening for AM related retinal toxicity was performed in 109/139 (78.4%) patients using AMs in the past 2 years. Out of the 30 patients who did not have a screening in the past 2 years: 4 patients had a screening in the past 5 years, 5 patients had a screening but longer than 5 years ago. For 21 patients we could not find records on ophthalmologic screening of whom 6 patients used a daily HCQ dosage of 200 mg.

Non-use of antimalarials

Table II shows the reasons for non-use of AMs. In most of the cases, AMs were either never prescribed without a documented reason or discontinued without a documented reason. The second most common reason for not using AMs was intolerance. None of the 7 patients who had 'quiescent disease' as a reason for non-use of AMs, had used any other DMARD or steroids. Reported intolerances were: non-specific/non-AM-related vision disturbances: 3, hair loss: 3, non-specific complaints: 3, gastro-intestinal complaints: 2, cardiomyopathy possibly due to HCQ: 1, joint pain: 1, dysuria: 1, mononeuritis multiplex: 1. One patient discontinued AM use because of documented HCQ related retinopathy. Prior to the detection of AM-related retinopathy, this patient used HCQ (daily dosage of 400 mg) for 11 years and ophthalmologic investigations performed yearly did not reveal abnormalities in the preceding years. Adjusted for length (1.65 m) and weight (53 kg) the daily dosage in this patient was 11.0 mg/kg lean body weight. Median duration of HCQ use in the group of 36 patients who discon-

tinued HCQ was 2 years (interquartile range: 0-7 years). Six patients discontinued HCQ after more than 10 years of use. The mean SDI in the 9 patients who never used any AM was 1.4 of which 5 had an SDI of 0.

Reported contraindications for initiating HCQ treatment were myasthenia gravis in 1 patient and 1 patient had been advised not to take HCQ due to a supposed interaction with cyclosporine. Other reported reasons to discontinue AMs were: during the treatment of lupus nephritis: 1, start of pre-transplantation phase: 1, remission of cutaneous manifestations: 1. In 1 patient HCQ was discontinued due to ineffectiveness with respect to treatment of arthritis.

Differences between antimalarial users and non-users

Disease manifestations and laboratory features of SLE patients according to the revised ACR criteria using or not using AMs are shown in Table III. In our cohort 42 patients had a history of biopsy proven lupus nephritis. In patients with biopsy proven lupus nephritis, the frequency of AM use was significantly lower compared to patients without biopsy proven lupus nephritis (23/42 patients, 54.8% *vs*. 116/148 patients, 78.4%) (p=0.002). Eight out of 9 patients who never used AMs, had a history of lupus nephritis, of whom 6 had lupus nephritis as initial symptom of SLE. As shown in Table I, both groups of AM users and non-users were comparable for age, sex, ethnicity, age at diagnosis and SLEDAI at the time of current study. Non-AM users had a significantly longer disease duration (p=0.004) and higher SDI (p<0.001). Logistic regression (Table IV) showed that a higher SDI (p=0.019) and biopsy proven lupus nephritis (p=0.024), but not disease duration (p=0.077) were significantly and independently associated with non-use of AMs.

Table II. Reasons for non-use of antimalarials among patients with systemic lupus erythematosus.

Reasons	Never used antimalarials (n=15), n (%)	Discontinuation of antimalarials (n=36), n (%)	Total (n=51), n (%)
No documented reason	9 (60)	11 (30.6)	20 (39.2)
Intolerance		16 (44.4)	16 (31.4)
Quiescent disease	2 (13.3)	5 (13.9)	7 (13.7)
Other		3 (8.3)	3 (5.9)
Patient refusal	2 (13.3)		2 (3.9)
Contraindication	2 (13.3)		2 (3.9)
Ineffective		1 (2.8)	1 (2.0)

Table III. Disease manifestations and laboratory features according to the revised ACR criteria in systemic lupus erythematosus patients using or not using antimalarials.

Features	Antimalarial use (n=139), n (%)	No antimalarial use (n=52), n (%)	p-value
Malar rash	54 (38.8)	24 (47.1)	0.308
Discoid lesions	21 (15.1)	11 (21.6)	0.292
Photosensitivity	95 (68.3)	36 (70.6)	0.767
Oral ulcers	65 (46.8)	23 (45.1)	0.838
Arthritis	109 (78.4)	40 (78.4)	0.998
Serositis	55 (39.6)	17 (33.3)	0.432
Nephrologic	41 (29.5)	24 (47.1)	0.024‡
Neuropsychiatric	7 (5)	6 (11.8)	0.104
Haematologic	128 (92.1)	46 (90.2)	0.678
ANA	139 (100)	52 (100)	1.000
Anti-dsDNA	106 (76.3)	43 (84.3)	0.232
Anti-Sm	34 (24.5)	7 (13.7)	0.278
ACA	39 (28.1)	11 (21.6)	0.655
LAC	42 (30.2)	20 (39.2)	0.440

ANA: anti-nuclear antibody; ACA: anti-cardiolipin antibody; LAC: lupus anticoagulant.
‡Significant values.

Table IV. Logistic regression of antimalarial use (dependent variable), clinical variables (independent variables).

Variables	B (SE)	Odds ratio	95% CI	p-value
SDI	-0.186 (0.079)	0.831	0.712 to 0.969	0.019
Lupus nephritis	-0.870 (0.386)	0.419	0.197 to 0.892	0.024
Disease duration, years	-0.037 (0.021)	0.964	0.925 to 1.004	0.077

SDI: systemic lupus international collaborating clinics damage index; B: regression coefficient; SE: standard error; 95% CI: 95% confidence interval.

Discussion

The main focuses of this study were the use of AMs, reasons for non-use, and dosage-related intolerance in our cohort. The most striking finding was that 87.4% of our patients used a higher daily HCQ dosage than the recommended 6.5mg/kg lean body weight in guidelines (15). Even when daily dosage was erroneously calculated according to body weight, 39 patients (38.7%) used more than the recommended dosage. However, only 15 out of 190 patients (7.9%) discontinued AMs in the past due to intolerance. Based on these data, we suppose higher dosages according to lean body weight than the recommended maximum might probably be well tolerated. We also showed that adjusting daily dosage according to weight instead of lean body weight poses the thread of overdosing AMs. Another way of determining the optimal daily dosage of HCQ might be through measurement of HCQ concentration in blood, although currently there is not enough evidence that increasing the HCQ dose leads to fewer flares (21).

We found that 73.2% of our patients were using AMs at their last visit, which percentage is comparable to the frequencies reported in previous studies (11, 17-19). Bultink *et al*. (27) published a cross-sectional study in 141 women with SLE, under treatment dur-

ing 2001–2005 at the clinics examined in this study (VUmc and Jan van Breemen Institute), and found that 49% used HCQ at that time. These data indicate that the newer insights into the beneficial effects of AMs in SLE are also translated into more frequent prescription in clinical practice. In fact, the far majority of our patients (91,6%) have used AMs at some time point during their disease.

However, there is still room for improvement: some reported intolerances could not always reasonably be attributed to AM use, *e.g.* joint pain and mononeuritis multiplex. In one case, an AM was discontinued during the treatment of lupus nephritis, while AMs have been shown to improve outcome in lupus nephritis (28). In another case an AM was not prescribed due to a supposed interaction with cyclosporine, while a clinical relevant adverse interaction between AMs and cyclosporine has not been shown (29).

Non-use of AMs in our cohort was mainly because of discontinuation due to intolerance (31.4%). Unfortunately, in 39.2% of the cases there was no documentation on the reason why AMs were discontinued or not prescribed. Absence of disease activity in patients with mild disease without organ damage was the reported reason for 7 patients for either discontinuation or not prescribing AMs. Currently, it is unknown whether AMs should be prescribed to patients with clinically and serologically quiescent disease, as no robust data are present showing that AMs can prevent accrual of damage in this specific group of patients. Hopefully, treat-to-target principles in SLE, that are currently in development, will aid physicians in how to optimally treat their patients (30).

We found that a history of lupus nephritis was significantly and independently associated with non-use of AMs in our cohort. A possible explanation for this finding might be that in the past it has been custom not to initiate or even to seize AMs in patients who developed lupus nephritis requiring treatment with high dose corticosteroids and immunosuppressive agents. The rationale behind this phenomenon was that AMs were considered as weak immunosuppressive agents, compared to the other immunosuppressive drugs initiated for lupus nephritis, and would not have a beneficial effect on outcome. Only in recent years the beneficial effects of continuing AMs during the treatment of lupus nephritis became clear (4). Our study shows that the frequency of AM use is still lower in patients with a history of lupus nephritis compared to patients without nephrologic complications (54.8% *vs*. 77.7%). In fact, we found that out of the 8 patients who never used AMs and had a biopsy proven lupus nephritis somewhere in their disease course, 6 had a lupus nephritis as presenting symptom and in one patient it was documented that HCQ was discontinued during the treatment of lupus nephritis.

We also found that higher SDI was significantly and independently associated with non-use of AMs. This finding is in line with previous studies on the protective effect of AMs on damage accrual in SLE (10, 11). Finally, non-use of AMs was significantly but not independently associated with longer disease duration, although a trend for such an association was found. This association probably reflects the non-use of AMs in the past, and the increased use of AMs in recent years. Another explanation may be that in some cases a prolonged use of AMs may be associated with adverse events, such as in patients with AM related retinopathy and cardiomyopathy.

Retinopathy is the most feared side-effect of AM use that occurs in approximately 1% after 5 years of use (14). In this study, only one patient developed AM related retinopathy. She had used a daily dose of HCQ of more than 6.5mg/kg lean body weight for more than 10 years, which are both known risk factors for retinal toxicity (15). To assess possible ascertainment bias regarding detected retinal toxicity we checked for ophthalmologic screenings in the past. We found that 84.9% of our patients had an ophthalmologic screening, of whom 78.4% in the past 2 years and in addition 2,9% in the past 5 years. Obviously, there is also room for improvement in ophthalmological screenings in our patients. However, despite the infrequent screenings in some patients, it appears that retinal toxicity due to AMs is a rare complication of AM use.

There are some limitations to this study. Unfortunately, it was not possible to retrieve the reason for withdrawal or not prescribing AMs in all patients. Furthermore, we could not calculate cumulative dosages of AMs, because changes in dosage and intermittent withdrawal were not always recorded, which is important to evaluate side-effects related to cumulative dosages.

In conclusion, this study showed that AM use in a Dutch cohort of SLE patients has improved in recent years, but is not yet optimal. Discontinuation due to side-effects is the most reported reason for non-use, although infrequently occurring. We also showed that patients with longstanding SLE and/or a history of lupus nephritis used AMs less frequently, while for the latter subgroup of patients the beneficial effects are most clear and even recommended in the current guideline. Thirdly, we have shown that AMs are frequently prescribed in dosages above the recommended 6.5 mg/kg lean body weight, but that these dosages seem to be well tolerated. Given the beneficial effects of AMs with respect to safety and tolerance, we encourage physicians to evaluate whether AMs can be initiated in non-users.

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