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Hydroxychloroquine in patients with systemic lupus erythematosus: how much is enough?

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ABSTRACT

Objective To assess the daily and weight-adjusted dosages of hydroxychloroquine (HCQ) and the effects on long-term remission in the Lupus-Cruces cohort.

Methods Observational study of routine clinical care data. We selected inception patients treated with HCQ with at least 5 years of follow-up. Prolonged remission was achieved when patients fulfilled definitions of remission in systemic lupus erythematosus remission criteria in five consecutive yearly visits. The associations between the weight-adjusted dose of HCQ during 5 years and prolonged remission were analysed. We also investigated the associations between prednisone doses, immunosuppressives (IS) and other antimalarial use with HCQ doses.

Results 150 inception patients fulfilled the inclusion criteria. The mean starting dose of HCQ was 206 mg/day. The mean weight-adjusted starting dose of HCQ was 3.1 mg/kg/day with no patients treated with doses ≥5 mg/kg/day. Treatment with HCQ was maintained during the whole 5-year follow-up time in 148 patients (98%). The mean dose of HCQ during the 5-year follow-up was 194.6 mg/day (2.9 mg/kg/day). 108 patients (72%) were in prolonged remission. The mean weight-adjusted dose of HCQ per patient did not differ between those who did and did not achieve prolonged remission (2.9 vs 3 mg/kg/day, p=0.5). The dose of prednisone per patient (mean 2.3 mg/day during the 5-year follow-up) did not differ according to the weight-adjusted dose of HCQ. The mean weight-adjusted HCQ dose during the whole follow-up was the same in patients treated or not with IS or with mepacrine.

Conclusions With the use of HCQ at stable doses of 200 mg/day (or 3.0–3.5 mg/kg/day) as the background therapy in patients with systemic lupus erythematosus, the majority of patients achieved prolonged remission.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Hydroxychloroquine (HCQ) is the cornerstone therapy in systemic lupus erythematosus (SLE), therefore every effort should be made to maintain it long-term.
⇒ The balance between macular toxicity (mostly related to daily doses >5 mg/kg/day) and efficacy is a matter of debate.
⇒ The reduction of HCQ dose from >5 mg/kg/day to <5 mg/kg/day can result in lupus flares.

WHAT THIS STUDY ADDS

⇒ With the use of mean stable HCQ dose of 3.0–3.5 mg/kg/day for most patients with mild, moderate or severe baseline lupus activity, the majority of them achieved prolonged remission.
⇒ Maintenance doses of prednisone were ≤5 mg/day in all cases.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our study supports the use of stable doses of 200 mg/day (or 3.0–3.5 mg/kg/day) of HCQ in patients with SLE.
⇒ Further comparative studies between stable doses lower and higher than 5 mg/kg/day could confirm these results.

INTRODUCTION

Hydroxychloroquine (HCQ) is the cornerstone of therapy for systemic lupus erythematosus (SLE) due to multiple beneficial effects including control of lupus activity, reduced damage accrual and increased survival.[1] Maculopathy can rarely occur, usually mild and in patients exceeding 10 years of use at doses >5 mg/kg/day, although it can happen earlier and at lower doses.[2] More recent data prove that the risk for maculopathy continues to decrease with lower doses even below the 5 mg/kg/day threshold.[3] Thus, the commonly prescribed 400 mg/day dose results excessive for many patients according to current recommendations,[4] however, concerns exist regarding the efficacy of lower doses.[5] In the Lupus-Cruces cohort, 200 mg/day has long been the standard of care[6] like other internal medicine departments in Spain with a large experience in the management of SLE.[7] The aim of this study is to assess the actual daily and weight-adjusted dosages of HCQ and the resultant effects on long-term remission in our inception patients.

Table 1 Description of the whole cohort and by baseline activity groups

Variable	Whole cohort (N 150)	Baseline activity			P value
		Mild (N 87)	Moderate (N 50)	Severe (N 13)	
Female, n (%)	121 (80.7)	73 (83.9)	38 (76.0)	10 (76.9)	0.496
Caucasian, n (%)	139 (92.7)	81 (93.1)	47 (94.0)	11 (84.6)	0.498
Age of diagnosis (years), mean (SD)	41.0 (14.9)	40.4 (14.3)	42.9 (16.6)	37.5 (11.2)	0.429
Weight (kg), mean (SD)	68.3 (14)	67.3 (13)	67.9 (15)	76.4 (19)	0.1
Smoking year 1, n (%)	42 (28.0)	25 (28.7)	12 (24.0)	5 (38.5)	0.570
Baseline immunological and clinical profile					
Anti-Ro, n (%)	48 (32.0)	26 (29.9)	19 (38.0)	3 (23.1)	0.477
Anti-La, n (%)	18 (12.0)	8 (9.2)	9 (18.0)	1 (7.7)	0.275
Anti-U_1 RNP, n (%)	31 (20.7)	18 (20.7)	9 (18.0)	4 (30.8)	0.599
Anti-Sm, n (%)	22 (14.7)	11 (12.6)	7 (14.0)	4 (30.8)	0.224
Anti-DNA, n (%)	84 (56.0)	36 (41.4)	35 (70.0)	13 (100)	<0.001
APL, n (%)	49 (32.7)	29 (33.3)	14 (28.0)	6 (46.2)	0.452
Hypocomplementaemia, n (%)	80 (53.3)	31 (35.6)	36 (72.0)	13 (100)	<0.001
Cutaneous, n (%)	91 (60.7)	57 (65.5)	27 (54.0)	7 (53.8)	0.360
Articular, n (%)	100 (66.7)	55 (63.2)	34 (68.0)	11 (84.6)	0.303
Serosal, n (%)	23 (15.3)	6 (6.9)	13 (26.0)	4 (30.8)	0.003
Haematological, n (%)	19 (12.7)	9 (10.3)	9 (18.0)	1 (7.7)	0.368
Thrombocytopenia, n (%)	10 (6.7)	6 (6.9)	3 (6.0)	1 (7.7)	0.968
Lymphopenia, n (%)	36 (24.0)	11 (12.6)	20 (40.0)	5 (38.5)	0.001
Nephritis, n (%)	20 (13.3)	0 (0)	8 (16.0)	12 (92.3)	<0.001
CNS, n (%)	2 (1.3)	1 (1.1)	1 (2.0)	0 (0)	0.832
Baseline SLEDAI, mean (SD)	6.0 (5.0)	2.8 (1.4)	8.1 (2.0)	18.9 (2.7)	<0.001
Prolonged remission, n (%)	108 (72)	67 (77)	34 (68)	7 (53)	0.16
Therapy other than HCQ					
Prednisone year 1, n (%)	110 (73.3)	54 (62)	46 (86)	13 (100)	0.001
Maximum prednisone dose year 1 (mg/day),* mean (SD)	12.8 (9)	10 (8)	12 (8)	26 (7.0)	<0.001
Average prednisone year 1 (mg/day),* mean (SD)	4 (2)	3.2 (2)	4.4 (2)	6.4 (2.4)	<0.001
Prednisone years 1–5, n (%)	125 (83)	65 (74)	47 (94)	13 (100)	0.003
Average prednisone years 1–5 (mg/day),* mean (SD)	2.3 (1.6)	2 (1.5)	2.5 (1.4)	3.9 (1.8)	<0.001
MP years 1–5, n (%)	67 (45)	26 (30)	28 (56)	13 (100)	<0.001
AZA years 1–5, n (%)	30 (20)	12 (14)	11 (22)	7 (54)	0.003
MTX years 1–5, n (%)	30 (20)	17 (20)	13 (26)	0 (0)	0.112
MF years 1–5, n (%)	20 (13)	3 (3.5)	9 (18)	8 (61)	<0.001
CYC years 1–5, n (%)	21 (14)	5 (6)	6 (12)	10 (77)	<0.001
Mepacrine years 1–5, n (%)	11 (7)	5 (6)	4 (8)	2 (15)	0.4
Belimumab years 1–5, n (%)	3 (2)	1 (1)	2 (4)	0 (0)	0.6
Rituximab years 1–5, n (%)	2 (1.3)	0 (0)	2 (4)	0 (0)	0.27

*In patients taking the drug.
Anti-DNA, DNA antibodies; Anti-La, anti-Sjögren's-syndrome-related antigen B, also called anti-SSB; Anti-Ro, anti-Sjögren's-syndrome-related antigen A, also called anti-SSA; Anti-Sm, anti-Smith; Anti-U_1RNP, anti-U_1 ribonucleoprotein; APL, antiphospholipid antibodies; AZA, azathioprine; CNS, central nervous system; CYC, cyclophosphamide; HCQ, hydroxychloroquine; MF, mycophenolate; MP, methylprednisolone; MTX, methotrexate; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

PATIENTS AND METHODS

Study design and patients

This is an observational study of routine clinical care data of the Lupus Cruces- cohort. All patients included in the database fulfilled the Systemic Lupus International Collaborating Clinics (SLICC) criteria for the classification of SLE.[8] We selected inception patients who were diagnosed after the year 2000 and with at least 5 years of follow-up. Patients not receiving HCQ during this period or those who died before completing 5 years of follow-up were excluded from the analysis.

Outcome measures

The main outcome was remission according to the definitions of remission in SLE (DORIS).[9] Remission was assessed once yearly (from years 1 to 5) after the diagnosis.

Table 2 Hydroxychloroquine therapy in the whole cohort and by SLEDAI groups

Variable	Whole cohort (N 150)	SLEDAI <6 (N 87)	SLEDAI 6–12 (N 50)	SLEDAI >12 (N 13)	P value
HCQ starting dose (mg/day), mean (SD)	206.0 (37)	205.8 (38)	204.0 (28)	215.4 (55)	0.615
HCQ starting dose (mg/kg/day), mean (SD)	3.1 (0.8)	3.2 (0.9)	3.1 (0.8)	2.9 (0.6)	0.561
HCQ dose years 1–5 (mg/day), mean (SD)	194.6 (36)	192.0 (40)	194.4 (20)	212.4 (54)	0.173
HCQ dose years 1–5 (mg/kg/day), mean (SD)	2.9 (0.8)	2.9 (0.8)	2.9 (0.7)	2.9 (0.6)	0.864
Time on HCQ years 1–5 (months), mean (SD)	58 (7)	57 (9)	59 (5)	60 (0)	0.602
Cumulative HCQ dose years 1–5 (g), mean (SD)	355.2 (66)	350.5 (73)	354.8 (37)	387.7 (99)	0.173

HCQ, hydroxychloroquine; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

Prolonged remission was achieved when patients fulfilled DORIS criteria in all five consecutive yearly visits.

In addition, we explored the associations between the different doses of HCQ, the doses of prednisone and the use of immunosuppressives (IS) and mepacrine.

Statistical analysis

Descriptive data were generated, using percentages, means and SD. All the analyses were stratified by the year of diagnosis, grouped in four different slots: 2001–2005, 2006–2010, 2011–2015, 2016–2018 and by the baseline SLE Disease Activity Index 2000 (SLEDAI 2K) score defined as mild (<6), moderate (6–12) and severe (>12) activity.[4]

Comparisons were made by χ^2 test, student's t-test, one-way analysis of variance or univariate linear regression, as appropriate.

RESULTS

Demographic and clinical profile at diagnosis

Three patients did not receive HCQ within the study period (one who refused to take the drug, one with a hereditary degenerative retinal condition who was treated with mepacrine instead and one in whom HCQ was not prescribed) and one patient died before the fifth year of follow-up. Therefore, 150 patients (97.4% of the inception cohort with at least 5 years of follow-up) were included. The baseline SLEDAI was similar across the four-time slots for SLE diagnosis (p=0.8).

The main demographic, clinical and therapeutic variables are summarised in table 1.

HCQ dosing

HCQ-related variables are summarised in table 2. The mean (SD) starting dose of HCQ was 206 mg/day (37.0), 96% of patients taking 200 mg/day. The starting dose of HCQ did not differ across the four-time slots (year 2001–2005, 206 mg/day; year 2006–2010, 202 mg/day; year 2011–2015, 211 mg/day; year 2016–2018, 200 mg/day; p=0.7).

The mean (SD) dose of HCQ during the 5-year follow-up was 194.6 mg/day (35.8). Only three patients (2%) received HCQ >300 mg/day (309, 316 and 395 mg/day, respectively). The mean (SD) weight-adjusted HCQ dose during the follow-up was 2.9 mg/kg/day (0.8). 99% received <5 mg/kg/day. All HCQ-related variables did not differ across the three baseline SLEDAI groups.

The mean (SD) weight-adjusted starting dose of HCQ was 3.1 mg/kg/day (0.8) with 98% of patients receiving ≤4.5 mg/kg/day. No patients were treated with doses ≥5 mg/kg/day. The mean weight-adjusted starting dose of HCQ was similar in all subgroups (year 2001–2005, 3.2 mg/kg/day; year 2006–2010, 3 mg/kg/day; year 2011–2016, 3.2 mg/kg/day; year 2016–2018, 3.1 mg/kg/day) and across baseline activity groups. Such doses remained substantially unchanged during the 5-year follow-up (table 3).

Remission and weight-adjusted HCQ doses

108 patients (72%) were in prolonged remission. The mean (SD) weight-adjusted initial dose of HCQ per patient was similar whether they achieved or not remission at year 1 (3.1 vs 3.2 mg/kg/day, respectively, p=0.46) or prolonged remission (2.9 vs 3 mg/kg/day, respectively, p=0.5). Analysing the different subgroups according to the year of diagnosis and the baseline activity (table 3), the weight-adjusted doses were similar.

HCQ, GC dose, IS and mepacrine

The mean dose of prednisone did not differ in relation to the weight-adjusted HCQ dose either during the first year (linear regression coefficient 0.004, p=0.86) or within the whole 5-year follow-up (linear regression coefficient 0.053, p=0.15). Likewise, the mean weight-adjusted HCQ dose during the whole follow-up was the same in patients treated or not with IS (2.9 mg/kg/day in both groups, p=0.9) or with mepacrine (3.3 vs 3.0 mg/kg/day, p=0.13).

Duration and discontinuation of HCQ therapy

Treatment with HCQ was maintained during the whole 5 years in 148 patients (98%) making a mean (SD) time on HCQ per patient of 58 months (7.0). HCQ was withdrawn after the first year in one patient by personal will, without toxicity. 26 patients spent a variable number of months off HCQ due to intermittent lack of adherence. Only in one patient was HCQ suspended for an increased number of drusen, although this was not considered by the ophthalmologists a clear sign of antimalarial toxicity.

Table 3 HCQ weight-adjusted dosage and remission by baseline activity and year of diagnosis

	HCQ starting dose (mg/kg/day), mean (SD)		
	Remission year 1	No remission year 1	P value
Whole cohort (n=150)	3.1 (0.7)	3.2 (1.1)	0.46
By SLE activity at baseline			
Mild activity (n=87)	3.1 (0.7)	3.5 (1.5)	0.18
Moderate activity (n=50)	3.1 (0.8)	3.0 (0.6)	0.69
Severe activity (n=13)	2.8 (0.67)	3.1 (0.61)	0.35
By year of diagnosis			
2001–2005 (n=31)	3.2 (0.5)	2.9 (0.8)	0.17
2006–2010 (n=45)	2.9 (0.7)	3.0 (0.4)	0.71
2011–2015 (n=53)	3.1 (0.9)	3.7 (1.5)	0.13
2016–2018 (n=21)	3.1 (0.6)	2.6 (0.09)	0.20
	HCQ year 1–5 dose (mg/kg/day), mean (SD)		
	Prolonged remission	No prolonged remission	P value
Whole cohort (n=150)	2.9 (0.7)	3.0 (2.7)	0.5
By SLE activity at baseline			
Mild activity (n=87)	2.9 (0.7)	3.0 (1.1)	0.58
Moderate activity (n=50)	3.0 (0.7)	2.9 (0.5)	0.92
Severe activity (n=13)	2.6 (0.67)	3.1 (0.54)	0.19
By year of diagnosis			
2001–2005 (n=31)	3.1 (0.5)	2.8 (0.6)	0.27
2006–2010 (n=45)	2.8 (0.8)	3.1 (0.7)	0.23
2011–2015 (n=53)	2.9 (0.7)	3.0 (1.2)	0.64
2016–2018 (n=21)	2.9 (0.8)	2.9 (0.4)	0.98

HCQ, hydroxychloroquine; SLE, systemic lupus erythematosus.

DISCUSSION

The analysis of our inception patients confirms that doses of HCQ of 200 mg/day have been used in the LupusCruces cohort for more than 20 years. The frequent use of methylprednisolone to treat flares and the early addition of IS completed our standard of care.[10] In this study, we found that patients treated with HCQ at sustained doses of 3–3.5 mg/kg/day achieved high rates of prolonged remission and also received low cumulative doses of oral glucocorticoids.

HCQ at 400 mg/day has been frequently prescribed worldwide, which is over 6.5 mg/kg/day for a 60 kg-average patient. Recently updated guidelines recommend keeping patients on HCQ under that limit,[4] however, studies in the SLICC cohort[11] and the Massachusetts General Hospital cohort[12] found an increased risk of flare among patients who reduced the daily dose of HCQ to <5 mg/kg/day.

It is expected that patients with reduced doses have lower blood levels of HCQ. However, the relation between both is not linear and is subjected to many interactions.[13] Very low HCQ levels are a good marker for poor adherence,[14] on the contrary, a French multicentre controlled trial failed to demonstrate a reduction of SLE flares among patients in whom the daily dose of HCQ was adjusted to blood levels.[15]

Antimalarials have very large volumes of distribution including aqua-soluble compartments and organs such as liver, heart and muscle, pigmented tissues and mononuclear cells,[13] with 45% of the daily dose of HCQ being stored in lean tissues, fitting a three-compartment model of distribution.[16] The concentration in the acidic compartments of organ-settled lymphocytes and other immune cells mediates the beneficial immunoregulatory effects of HCQ.[16] Such tissue concentrations are not well related to either blood levels or daily doses. Actually, reaching a steady state within the target organs may take several months which can be related to the slow onset of the effect of antimalarials.[13] Once this state has been achieved at a given dose, the brisk reduction in the daily dosage, for instance, from 400 to 200 mg/day, the scenario of those studies finding a high rate of lupus reactivation with lower doses,[11 12] could cause an imbalance in the tissue levels of HCQ and thus promote flares.[13]

Our results support this hypothesis. Most patients on stable doses of 200 mg/day (or 3.0–3.5 mg/kg/day) remained well-controlled long term with maintenance doses of prednisone ≤2.5 mg/day, combined, if needed with IS and/or mepacrine. Weight-adjusted doses of HCQ did not differ between patients with different baseline activities or achieving or not prolonged remission. The doses of HCQ were stable in our unit across the 17 years of entering the cohort; in fact, most patients included in our previous studies showed the beneficial effects of HCQ on survival, thrombosis and cardiovascular damage, cancer and infections[13] were receiving 200 mg/day. As expected, ocular toxicity has not been observed in patients treated with HCQ for more than 11 years.[6] Indeed, preserving long-term therapy with HCQ is crucial to assure its many beneficial effects beyond the control of SLE activity.[1 3 4] For that, avoiding toxicity is the major goal.

Our main limitation is that we could not compare the clinical course of patients treated with doses lower and

higher than 200 mg/day or 5 mg/kg/day. However, our remission rates can be compared favourably with patients from other groups receiving 400 mg/day.[11 12] No differences in the dose of HCQ were found among patients who received additional drugs. Also, most of our patients were white and non-obese; while no relevant differences have been found in the pharmacokinetics of antimalarials regarding race,[16] black patients may present with more severe forms of disease. In addition, obesity may influence the body distribution of HCQ.[17]

In conclusion, with the use of HCQ at stable doses of 200 mg/day (or 3.0–3.5 mg/kg/day) as the background therapy, more than 70% of inception patients with SLE in our cohort achieved prolonged remission. While data on the safety of such doses are solid,[2 3] our results also substantiate their efficacy, however, comparative studies of stable doses of 200 versus 400 mg/day of HCQ would be needed to confirm our findings.

Correction notice This article has been corrected since it was published Online First. Affiliation of VM-T has been corrected.

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Contributors GR-I was the principal investigator of this study, contributed to study design, performed the statistical analysis, drafted and reviewed the manuscript and is the guarantor. DP-R, FA, VC-R and VM-T collected data and reviewed the manuscript. IR-A and DM-I contributed to study design and reviewed the manuscript. LA drafted and reviewed the manuscript. The work has been approved by all authors.

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Patient consent for publication Not applicable.

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