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ABSTRACT. ***Objective.*** To assess whether hydroxychloroquine (HCQ) prevents early damage in patients with systemic lupus erythematosus (SLE).

Methods. We updated an existing systematic review of literature on clinical effects of HCQ in patients with SLE. We conducted a nested case-control study embedded in an inception cohort of patients with SLE. Systemic Lupus International Collaborating Clinics Damage Index (SDI) at 3 years was considered as our primary outcome. Patients with SDI > 0 at 3 years were considered cases and patients with SDI = 0 were controls. Cases and controls were first compared by univariate analysis. Then conditional logistic regression models adjusting for potential confounders were done to study the effect of HCQ on damage accrual.

Results. Included in the analysis were 481 patients who had 3 or more years of followup. Out of this cohort, we could match 151 cases with 151 controls. Univariate analysis identified age, the use of any immunosuppressive drugs, HCQ, and cumulative dose of steroids as significant covariates associated with damage accrual. In multivariate analysis, the use of HCQ remained significantly associated with less damage (OR 0.34, 95% CI 0.132–0.867), while age (OR 1.05, 95% CI 1.027–1.078) and a variable combining SLE activity and steroid dose (OR 1.73, 95% CI 1.306–2.295) were associated with damage at 3 years.

Conclusion. We demonstrated that HCQ use was associated with less damage at 3 years after diagnosis of SLE when attention was given and adjustment done for disease activity and steroid dose, duration of disease, and calendar year of diagnosis. (First Release April 15 2013; J Rheumatol 2013;40:831–41; doi:10.3899/jrheum.120572)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS OUTCOMES RESEARCH
DISEASE ACTIVITY HYDROXYCHLOROQUINE DAMAGE

Systemic lupus erythematosus (SLE) is an autoimmune systemic illness characterized by acute and chronic inflammation of multiple organs. Antimalarial (AM) drugs, mainly hydroxychloroquine (HCQ), have been commonly prescribed in SLE to treat constitutional symptoms, rashes, and arthritis, and to prevent flares[1]. The

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immune-modulatory effect of AM is mediated by several mechanisms including antagonizing Toll-like receptor (TLR) activation, possibly by altering pH or through competitive inhibition. This can result in inhibition of interferon-α (IFN-α) expression and activation of multiple IFN-α-mediated pathways[2]. Although processing of low-affinity antigens (e.g., self-antigens) is blocked, the immune response against high-affinity antigens (e.g., bacterial peptides) is not impaired, which results in an effective immunomodulation without immunosuppression[3].

Despite the extensive use of AM in the treatment of SLE for decades, their numerous beneficial effects have only been demonstrated in recent years[2]. Ruiz-Irastorza, *et al* performed a systematic review of literature on clinical efficacy and side effects of AM in SLE, and given their wide-spectrum benefits and overall safety, suggested that these agents should be used in all patients with SLE[1]. In that review, 11 studies were identified supporting the beneficial effects of AM on SLE disease activity[4,5,6,7,8,9,10,11,12,12a,12b], 6 on thrombosis[13,14,15,16,17,18], 2 on organ damage[19,20], 2 on survival[16,21], 9 on lipid profile[22,23,24,25,26,27,28,29,30], and 4 on bone metabolism. That review showed that large series have consistently demonstrated the absence of serious adverse events even after prolonged use[1]. This emerging evidence supporting the use of AM in SLE has changed the practice pattern toward more frequent use of HCQ in patients with SLE[31].

Survival of patients with SLE has improved significantly over time[32]. As patients with SLE live longer, cumulative damage has become an important outcome[33]. Current evidence indicates that damage accrual occurs within the first few years after disease onset (mean of 3.8 yrs)[34].

Organ damage profoundly affects patients' functional and psychosocial state and health-related quality of life. Therefore, it is extremely important to identify predictors of damage and protective factors to prevent this irreversible sequel, aiming to improve survival, function, and health-related quality of life in these patients[32].

In 2005, Fessler, *et al* demonstrated a protective role for HCQ against damage accrual in patients with SLE enrolled in a prospective cohort (LUMINA), with baseline disease duration of up to 5 years[19]. In that study, damage accrual over time was compared in patients who were taking HCQ at baseline with patients who were not taking this medication, and demonstrated a protective effect[19]. More recently, Lopez, *et al*[35] analyzed data from another prospective SLE cohort (University College Hospital, London, Lupus Clinic) to assess the association between disease activity and damage accrual. They evaluated potential predictors of damage, and HCQ was protective in the univariate analysis, but this effect was not observed when the analysis was adjusted for other confounders[35].

Antimalarial drugs have traditionally been used for the treatment of mild to moderate SLE, particularly prior to the widespread use of these agents in recent years. This may lead to confounding by indication when studying the benefits of AM drugs in a longitudinal observational study in which treatments are not randomized. Indeed, patients with milder disease who were typically treated with AM drugs would naturally accrue less damage compared to those with severe multiorgan involvement. Fessler, *et al*[19] used a statistical matching technique that attempts to estimate the effect of AM drugs by accounting for the covariates that predict receiving it in the first place. This technique, called propensity score analysis, attempts to address the problem of confounding by indication. The study by Lopez, *et al* on the other hand used multivariate analysis to adjust for potential confounders[35,36].

Evidence for the beneficial effects of AM continues to grow. To collect and review the existing data, we updated the systematic review performed by Ruiz-Irastorza, *et al*[1]. It was found that the effect of HCQ on damage accrual during the initial years after diagnosis of SLE has not been evaluated. To capture the treatment effect in the early stage of disease, we conducted a nested case-control study in a large inception cohort where patients were enrolled at the time of diagnosis and we assessed the outcome, i.e., damage at 3 years. We matched case-control pairs by calendar year of diagnosis and severity of disease for the possibility of confounding by practice patterns or by treatment indication.

MATERIALS AND METHODS

Literature review. A comprehensive systematic review performed by Ruiz-Irastorza, *et al*[1] published in 2010 included English literature between 1982 and 2007, from Medline and Embase databases. We used the same search strategy and reviewed the literature between January 2007 and October 2012 from the same databases (Appendix 1 and 2). We selected clinical trials and observational studies, including adult patients, in which the clinical effects and/or toxicity of AM were analyzed. Case reports were excluded except for toxicity reports.

Study population. An inception cohort of patients with a diagnosis of SLE made within 1 year of enrollment between 1970 and 2009 was identified from the University of Toronto Lupus Clinic database. Ethical review and approval from the University Health Network Research Ethics Board were implemented in creating this database and participants' informed consent was collected at enrollment. In this cohort, diagnosis was based on fulfilling 4 or more of the 1971 or 1982 American College of Rheumatology (ACR) classification criteria[37], or 3 ACR criteria plus having a diagnostic histological lesion of SLE (on renal or skin biopsy). Patients with at least 2 visits who had been followed for at least 3 years were included in the current study.

Clinical variables. Demographic information included ethnicity, sex, and age at baseline, education status (finished high school), and calendar year of diagnosis. Disease activity was assessed by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K)[38] and damage was measured by the Systemic Lupus International Collaborating Clinics Damage Index (SDI)[39,40,41]. Other clinical variables included the adjusted mean SLEDAI (AMS), which is a valid measure of the average SLEDAI over the period of observation[42], and the maximum SLEDAI in the first 3 years. We limited our measure of AM exposure to that of HCQ because that is by far the most commonly used AM drug in our center. Treatment variables included dichotomous variable (whether used during the first 3 years) for HCQ, use of immunosuppressive drugs (any of azathioprine,

methotrexate, cyclophosphamide, mycophenolate mofetil, cyclosporine), and steroids. Because azathioprine is the most often used immunosuppressive drug in our cohort, we also studied azathioprine use alone. Duration of HCQ exposure (in months) during the first 3 years was also addressed as one of our independent variables.

Outcome variable and matching procedure. Our outcome of interest was damage (SDI) at 3 years. SDI was recorded in the database annually for all patients and was zero by definition at baseline. A case-control study was performed to control for the known confounders, especially disease activity and severity. We defined as cases all patients with SDI > 0 at 3 years. Controls were defined as patients with an SDI of zero at 3 years. Patients who missed the Year 3 visit but their subsequent SDI scores were zero were also considered controls. We performed an in-depth chart review to document the SDI at Year 3 for patients who missed the Year 3 followup but had a subsequent SDI > 0 to determine the time at which damage had developed. For each case, 1 control was matched based on disease severity as defined by the highest SLEDAI score over the study period and the calendar year of diagnosis. This practice would minimize the confounding effect of practice pattern change over time toward more frequent use of AM agent in patients with SLE.

Statistical analysis. Descriptive statistics were generated for cases and controls at baseline. Univariate conditional logistic regression was performed on each potential predictor of the outcome SDI. We then constructed multivariable conditional logistic regression models to study the effect of HCQ use on the development of damage while adjusting for age, sex, ethnicity, AMS, azathioprine use, and cumulative steroid dose. AMS and cumulative steroid dose were found to be statistically correlated (r = 0.36). To capture the overall contribution of these variables as a proxy for severity of disease during the followup period, we performed 2 sets of models: one using each variable AMS and steroid dose separately and another using a variable that combined the doses. For that second model, we created a new variable combining categories of AMS scores and steroid dose. First we verified the normal distribution of AMS in cases and controls. Then we categorized AMS and cumulative steroid dose into quartiles. For AMS (throughout the first 3 years of followup), we defined our 4 categories as AMS of < 3, ≥ 3 and < 6, ≥ 6 and < 9, and ≥ 9, and assigned scores of 1, 2, 3, and 4 to each, respectively. Similarly for cumulative steroid dose (gram), we categorized patients based on this variable's quartiles into 4 groups of 0, > 0 and < 9, ≥ 9 and < 18, and ≥ 18 g, with scores of 1, 2, 3, and 4 assigned to each, respectively. The summation of each pair of these subscores for an individual patient comprised the composite variable for that person, e.g., for a patient whose AMS in 3 years was 4 and the cumulative dose of steroid was 8 g, the index variable would be 4 (2 + 2).

Similar models were built to assess the effect of HCQ treatment duration on SDI adjusted for the above confounders. The statistical software SAS (version 9) was used for all statistical analyses and the significance level was set at 5%.

RESULTS

Literature review. Our search identified 1550 papers. After reviewing titles and abstracts, 58 papers were selected for full review. Forty-seven papers were included in the final review. Adverse events were assessed in 14 studies including 11 case reports[43,44,45,46,47,48,49,50,51,52,53,54,55,56] (Appendix 3). We found further evidence supporting the findings of the systematic review by Ruiz-Irastorza, *et al*[1] for thrombosis[57,58,59,60,61], survival[21,33,62,63], disease activity[47,64,65], lipid profile[17,28,51,66,67,68,69,70], and damage[35,36,71,72,73,74,75,76], while we found evidence for delayed SLE onset[77], reduced major infection rate[78], and possible protective effect on malignancy[79], with the use of AM. We updated the reports on toxicity and did not find new alarming signals. Overall, our literature review reinforces the conclusions of Ruiz-Irastorza, *et al*[1].

Main analysis. Our study population consisted of an inception cohort of 685 patients. Of those 685, 481 patients had 3 or more years of followup and were included in further analysis. Of this cohort, 174 were potential cases and 307 were identified as potential controls. We were able to match 151 cases with 1 control each (151 pairs) based on the calendar year of diagnosis (± 3 yrs) and maximum SLEDAI (< 2 points of that of the matched case). Baseline characteristics of cases and controls and the results of the univariate analyses are shown in Table 1. The distribution of patients in each AMS and cumulative steroid dose category is shown in Table 2.

As expected by design, AMS and maximum SLEDAI in the 2 groups were not significantly different. Mean age was higher among cases. Univariate analyses identified the use of any immunosuppressive drugs including azathioprine (OR 2.71, 95% CI 1.55–4.72, p = 0.0005) and azathioprine alone (OR 2.75, 95% CI 1.55–4.87, p = 0.0005) significantly associated with an increased risk of damage at Year 3, while the use of HCQ (OR 0.33, 95% CI 0.15–0.74, p = 0.0071) was associated with a reduced risk. The longer duration of HCQ therapy seemed to be protective; however, the OR was almost 1 (OR 0.977, 95% CI 0.958–0.997, p = 0.0254). Interestingly, the majority of cases and controls had not received HCQ during the first 3 years.

Table 3 shows the results of our multivariate model that includes AMS and cumulative steroid dose as separate variables. Table 4 demonstrates the additional model we created based on the composite variable SLE activity and steroid dose. In the multivariate analyses, HCQ use was associated with less damage at 3 years (OR 0.34, 95% CI 0.132–0.838) and the effect of azathioprine use was no longer significant. The beneficial effect of HCQ on damage at 3 years remained significant in the additional model (OR 0.34, 95% CI 0.132–0.867; Table 4). The "Lupus activity and steroid dose" variable was independently associated with an increased risk of damage (OR 1.73, 95% CI 1.306–2.295), and age remained significant (OR 1.05, 95% CI 1.027–1.078) in this model.

When the variable "HCQ use" was replaced with the variable "Duration of HCQ therapy" as a predictor, this variable was not significant in the multivariate models that included AMS and cumulative steroid dose (OR 0.98, 95% CI 0.96–1.003) or the composite SLE activity and steroid dose variable (OR 0.98, 95% CI 0.96–1.005; data not shown).

DISCUSSION

In this nested case-control study, we demonstrated that HCQ was associated with less damage as early as 3 years after disease onset. With improved management, patients with

Table 1. Characteristics of cases and controls and univariate analysis for risk factors associated with damage accrual in patients with systemic lupus erythematosus (SLE).

Characteristic	Cases, n = 151	Controls, n = 151	OR (95% CI)	p
Age, yrs, mean ± SD	38.8 ± 14.3	34.3 ± 12.9	1.03 (1.01, 1.05)	0.0048
Female, n (%)	124 (82.1)	133 (88.1)	0.65 (0.36, 1.21)	0.1731
White, n (%)	117 (77.5)	110 (73.3)	1.28 (0.76, 2.16)	0.3551
Finished high school, n (%)	99 (83.2)	110 (88.7)	0.77 (0.34, 1.75)	0.5328
AMS in the first 3 yrs	6.5 ± 4.4	6.0 ± 4.3	1.04 (0.97, 1.12)	0.2632
Maximum SLEDAI-2K in the first 3 yrs	14.9 ± 8.2	14.7 ± 8.2	1.08 (0.95, 1.23)	0.2513
Used immunosuppressive drug in the first 3 yrs (%)	69 (45.7)	40 (26.5)	2.71 (1.55, 4.72)	0.0005
Used azathioprine in the first 3 yrs (%)	59 (39.1)	31 (20.5)	2.75 (1.55, 4.87)	0.0005
Cumulative dose of steroids (g) in the first 3 yrs, median (Q1, Q3)	11.9 (3.4, 23.2)	5.0 (0.0, 12.9)	1.06 (1.03, 1.09)	0.0001
Used HCQ in the first 3 yrs (%)	38 (25.2)	54 (35.8)	0.33 (0.15, 0.74)	0.0071
Duration of HCQ use, mo, in 3 yrs, median (Q1, Q3)	0.0 (0.0, 6.9)	0.0 (0.0, 27.8)	0.977 (0.958–0.997)	0.0254

AMS: adjusted mean SLEDAI (mean ± SD); SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index; Q: quartile; HCQ: hydroxychloroquine.

Table 2. Distribution of patients in 4 categories of cumulative steroid dose and AMS [adjusted mean SLEDAI (Systemic Lupus Erythematosus Disease Activity Index)].

Cumulative Steroid Dose, n = 302		Adjusted Mean SLEDAI, n = 299 (3 missing)	
Category (Quartiles)	Frequency, n (%)	Category (Quartiles)	Frequency, n (%)
1 (dose = 0 g)	61 (20)	1 (AMS < 3)	85 (28)
2 (0 < dose < 9 g)	110 (37)	2 (3 ≤ AMS < 6)	67 (22)
3 (9 ≤ dose < 18 g)	70 (24)	3 (6 ≤ AMS < 9)	69 (23)
4 (18 g ≤ dose)	58 (19)	4 (9 ≤ AMS)	81 (27)

Table 3. Multivariate analysis for risk factors associated with damage accrual in patients with SLE.

Variables	OR (95% CI)	p
Age, yrs, at baseline	1.05 (1.023, 1.072)	< 0.0001
Being female	0.41 (0.192, 0.901)	0.0261
White	1.74 (0.905, 3.342)	0.0970
Ever used azathioprine in the first 3 yrs	1.67 (0.814, 3.415)	0.1625
AMS in the first 3 yrs	1.11 (1.010, 1.231)	0.0305
Steroid — cumulative dose in the first 3 yrs	1.07 (1.029, 1.108)	0.0006
Used HCQ in the first 3 yrs	0.34 (0.139, 0.838)	0.0190

SLE: systemic lupus erythematosus; AMS: adjusted mean SLEDAI; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; HCQ: hydroxychloroquine.

Table 4. Multivariate analysis for risk factors associated with damage accrual in patients with SLE (including the lupus activity steroid dose variable).

Variables	OR (95% CI)	p
Age, yrs, baseline	1.05 (1.027, 1.078)	< 0.0001
Being female	0.54 (0.258, 1.124)	0.0993
White	1.84 (0.941, 3.591)	0.0745
Ever used azathioprine in the first 3 yrs	1.99 (0.997, 3.953)	0.0510
Lupus activity and steroid dose variable in the first 3 yrs	1.73 (1.306, 2.295)	0.0001
Used HCQ in the first 3 yrs	0.34 (0.132, 0.867)	0.0240

HCQ: hydroxychloroquine.

SLE live longer[33] but at the cost of an increased chance of developing premature comorbidities or damage. Any protective measures against damage accrual can potentially affect patients' quality of life and longterm outcomes.

The clinical efficacy and adverse events of AM were demonstrated in an extensive review that supported beneficial effects of these agents on SLE disease activity, survival, damage, thromboembolic events, lipid profile, and bone metabolism[1]. Our updated search identified supporting evidence for clinical efficacy of HCQ in SLE published over the past 5 years in favor of improvements in survival[21,33,62,63], disease activity[64,65], lipid profile, glucose control, metabolic syndrome[17,28,66,67,68,69,70], and prevention of thromboembolic events[31,57,58,59,60,61]. Eight studies evaluated the effect of AM on damage. Three[74,75,76] of 4 studies[72,74,75,76] assessing renal damage and outcome of lupus nephritis showed beneficial effects. One found longer time to integument damage[36] and 1 showed longer time to neuropsychiatric damage[71]. Two studies focused on the effect of HCQ on the fetus (Appendix 4). Two studies assessed

overall damage (SDI) as the main outcome[35,73]. Petri, *et al* considered the last available visit SDI as the main outcome when they analyzed data on 2054 patients. About a third of those patients were enrolled within 1 year of disease onset and 27% had disease > 5 years at enrollment. The use of AM was associated with less damage but when adjusted for confounders in multivariate analysis, only age and steroid use remained significant (HCQ HR: 0.9, 95% CI 0.7–1.0, p = 0.06)[73]. The primary objective of the Lopez, *et al* study was to assess the association between disease activity and new damage (SDI change ≥ 1) in 350 patients with SLE, i.e., a number of these patients already had damage at the beginning of the followup. Disease duration varied from 0 to 34 years (median 6 yrs). The use of HCQ was not significant in multivariate analysis using Cox proportional hazards models[35].

The beneficial effect of HCQ on cumulative damage was previously shown in 2 other studies[19,20]. One had a small sample size, and the possibility of confounding by indication was not considered in the analysis[20]. In the more recent study, Fessler, *et al* showed that HCQ use at baseline was associated with a reduced risk of developing new damage (HR 0.73, 95% CI 0.52–1.00, p = 0.05) in 518 patients with SLE for ≤ 5 years who did not have damage at baseline[19]. The disease duration at baseline in this study was up to 5 years. In patients who had no damage at study entry, HCQ use decreased the risk of damage accrual (HR 0.55, 95% CI 0.34–0.8, p = 0.0111). This was not observed in those receiving HCQ who had damage. Propensity score was used to adjust for potential confounders[19]. Propensity score analyses improve the risk of confounding by indication but will not be optimal if all relevant variables are not included in the propensity score model, and remaining unmeasured confounding may still be present and cause bias[80].

Among existing studies, our analysis is, to our knowledge, the only one assessing early damage accrual in an inception SLE cohort. Our study supports the results from Fessler, *et al*[19,20] using different analysis, which allowed us to adjust for disease severity, duration of disease, and calendar year of diagnosis.

Considering the study design and the nature of observational studies in general, our work has certain limitations. Despite our best efforts to minimize confounding, by matching cases and controls based on the main confounders and adjusting our final models for other possible confounders, it is still possible that our results are affected by residual (hidden) confounding. This could explain the association observed between the use of azathioprine and damage accrual in the univariate analysis that is no longer significant in the multivariate analysis. Residual confounding is one of the major limitations researchers face with the analysis of observational data. A controlled clinical trial would be ideal to prove the effect of HCQ use but such a trial is unlikely to be conducted considering ethical restrictions on the use of placebo when several benefits have been proven for HCQ in SLE.

We were interested in evaluating the effect of the treatment duration (HCQ exposure) on this important outcome. We found an association in univariate analysis but not in multivariate analysis. This could be due to the small numbers of treated patients among both cases and controls. We also tried to determine whether there was any specific organ damage that was prevented in HCQ users by comparing SDI items in users with nonusers. This analysis was again limited, owing to the small number of HCQ users among cases, and was only significant for pulmonary fibrosis (data not shown).

Compared to other conventionally used immunomodulators, HCQ is inexpensive, widely available, well tolerated, and has low toxicity. Our findings are in support of the wide and early use of this medication in patients with SLE in the absence of contraindications.

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APPENDIX 1. The search strategy[1]. [References for all appendices follow Appendix 4.]

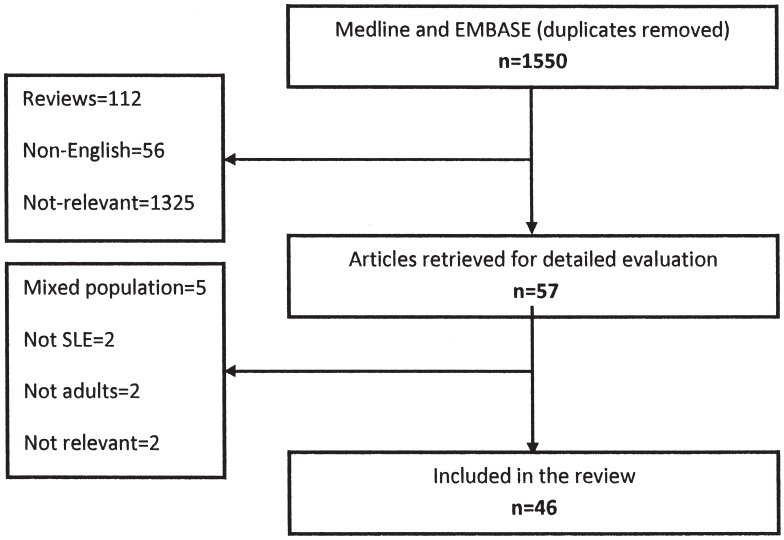
MEDLINE using the PubMed web page:

1- ("antimalarials [Mesh]" OR "chloroquine [Mesh]" OR "hydroxychloroquine [Mesh]")
2- "lupus erythematosus, systemic [Mesh]"
3- 1 and 2 Filters:Publication date from 2007/01/01

EMBASE using the OvidSP web page:

1- Exp "systemic lupus erythematosus (disease management OR drug therapy OR therapy OR side effects)"
2- ("antimalarials" OR "chloroquine" OR "hydroxychloroquine").mp.
3- 1 and 2
4- limit 3 to yr="2007-current"

Literature search diagram:



APPENDIX 2. Overview of included studies - Clinical effects

Author/year	Type of study	N	AM	Country/cohort	Main outcome	AM effect
Disease activity						
Willis 2012[2]	Longitudinal prospective	35	HCQ	USE (LUMINA)	Cytokine and disease activity levels	HCQ ↓ SLAM-R scores (p=0.0157), and ↓SLAM-R after HCQ therapy correlated with ↓ IFN-α (p=0.0087).
Shinjo 2009[3]	Retrospective	57	CQ+HCQ	Brazil	Remission	AM associated with remission: (OR =12.91; 95% CI 2.87–58.13)
Thrombosis						
Broder 2012[4]	Cross-sectional	90	HCQ	USA	Persistent positive LAC and/or aPL ≥ 40 U	↓risk (OR= 0.21, 95% CI 0.05- 0.79, p = 0.02)
Jung 2010[5]	Nested case-control	482	CQ+HCQ	Canada	Thromboembolic event	↓risk (OR= 0.31, 95% CI 0.13-0.71)
Becker-Merok 2009[6]	Prospective cohort	158	HCQ	Norway (Tromso)	Vascular events †	↓risk : OR =0.30; (95% CI 0.12–0.85)
Kaiser 2009[7]	Retrospective cohort	1930	HCQ	USA	Thromboembolic event	↓risk (OR= 0.62, p = 4.91×10^{-4})
Tektonidou 2009[8]	Prospective cohort	288	HCQ	Greece	Thrombotic event	↓ 1% risk of developing thrombosis per 1 month of treatment (HR per 1 month = 0.99)
Choojitaro 2008[9]	Cohort- prospective	67	HCQ+CQ	Thailand	Vascular thrombosis [β]	↓risk (OR = 0.18; p =0.034)
Survival						
Feng-2011[10]	Retrospective	1956	HCQ/CQ	China	Death	↓risk : HR=0.62 (95% CI 0.43-0.88, p=0.008)
Shinjo 2010[11]	Prospective cohort	1480	HCQ+CQ	GLADEL	Death	↓ Mortality by 38% (HR 0.62, 95% CI 0.39–0.99) Mortality was lower with longer AM use duration
Urowitz 2008[12]	Prospective cohort	1241	HCQ+CQ	Canada	Death	↓risk: HR=0.58 95% CI (0.39 0.87) p= 0.009
Alarcon 2007[13]	Nested Case-control	608	HCQ	LUMINA	Death	↓risk : OR= 0.128 (95% CI 0.054- 0.301)
Damage						
Lopez 2012[14]	Prospective cohort	350	HCQ	UK	SDI≥1, SDI≥3, renal SDI≥1, CNS SDI≥1, CV, pulmonary or MSK SDI ≥1; mortality	HR<1 but NS when adjusted in multivariate analysis, hence not protective
Okpechi 2012[15]	Retrospective	42	CQ	South Africa	Composite outcome: ESRD or↑ Cr x2BSL in patients with mLN*	NS‡ association with the composite end points (P = 0.05), CQ improved renal survival (P = 0.007).
Petri 2012[16]	Prospective	2054	HCQ	USA	SDI at last available visit	↓ damage risk but when adjusted for other factors age and steroid use were only significant predictors (HCQ : 0.9 (0.7–1.0) 0.060)
Pons-Estel 2012[17]	Nested case-control	796	CQ+HCQ	GLADEL	Persistent proteinuria or the presence of cellular casts	↓risk of renal damage (OR 0.39, 95% CI 0.26, p=0.58)
Pons_Estel 2010[18]	Prospecitve	580	HCQ	LUMINA	Time to integument damage & integument damage at 5 yr	↑time to integument damage: HR=0.23; 95% CI 0.12–0.47. ↓probability of integument damage at 5 y (5% vs 24%) (p<0.0001)
Gonzalez 2009[19]	Prospective cohort	632	HCQ	LUMINA	Time to NP[£] damage	↓risk :HR=0.58; 95%CI: 0.36-0.93
Pons_Estel 2009[20]	Prospective cohort	203	HCQ	LUMINA	Renal damage index SDI>0	↓risk: HR: 0.12, 95% CI 0.02-0.97, p = 0.0464
Siso 2008[21]	Case series	206	HCQ+CQ	Spain	Outcome of Lupus nephritis /survival	↓ ESRD: HR 0.294, CI 95% 0.026–1.009, p = 0.05 ↓infection and thrombosis ↑survival: HR 0.233, CI 95% 0.051–0.981,p = 0.042
Time to SLE onset						
James 2007[22]	Retrospective cohort	130	HCQ	USA	Time between initial symptoms and SLE classification	HCQ use prior to diagnosis increased (p= 0.018) time between the initial clinical symptom and SLE classification compared to no HCQ (median time: 1.08 vs 0.29 years)
Metabolic effects						
Chong 2011[23]	Cross-sectional , case-control	100[φ]	HCQ	China	Cholestrol components (LDL, HDL, TC[ψ])	Hydroxychloroquine (HCQ) treatment was associated with lower TC, LDL-c and HDL-cl
Rossoni 2011[24]	Cross-sectional	60	CQ, HCQ	Brazil	Cholesterol levels	No significant effect on TC, HDL and BMI
Nikpour 2010[25]	Prospective cohort	1260	CQ, HCQ	Canada	TC	↓TC† Est=-0.42 95%CI (-0.53, -0.32) p < 0.0001
Penn 2010[26]	Cross-sectional	149	HCQ	USA	Fasting glucose and insulin sensitivity	Fasting serum glucose and insulin resistance was lower in HCQ users
Cardoso 2008[27]	Cross-sectional	185	HCQ,CQ	Brazil	Dyslipoproteinemias	↓ hypertriglyceridemia OR : 0.44, 95% CI: 0.22–0.90
Sabio 2008[28]	Cross-sectional	160	HCQ	Spain	Metabolic syndrome	↓metabolic syndrome: OR: 0.192, 95%CI: 0.061–0.605, p=0.003
Sachet 2007[29]	Cross-sectional	20	CQ	Brazil	HDL-c, VLDL-c, LDL-c levels	lower Total and LDL-c in CQ group
Infection						
Ruiz-Irastorza 2009[30]	Nested case-control	249	CQ+HCQ	Spain	Major infection	↓infection rate : OR = 0.06, 95% CI = 0.02 - 0.18
Neoplasm						
Ruiz-Irastorza 2007[31]	Prospective cohort	235	CQ+HCQ	Spain	Development of a new neoplasm	↓risk of a new neoplasm: 0.15 (0.02-0.99) p=0.049

HCQ=Hydroxychloquine; CQ=Chloroquine; AM= Antimalarials; LAC= Lupus Anti-Coagulants; aPL: anti-phospholipid antibody; † Vascular Events (VE) were classified as atherothrombotic, venous thrombotic, arterial thrombotic or tissue loss inducing vasculitis; *mLN=membranous lupus nephritis; ‡ NS=not significant; £ NP= Neuropsychiatric ; [ψ]TC=total cholesterol; [φ]100 quiescent Lupus Nephritis and 100 controls; NL=Neonatal Lupus; [β]all pts had ≥ 1 +v aPL; BSL=baseline;

APPENDIX 3. Overview of included studies- Adverse events

Author/year	Type of study	N	AM	Country/ cohort	AM toxicity
Lee 2012[32]	Case report	1	HCQ	South Korea	Retinopathy combined with retinal pigment epithelium (RPE) detachment
Hsu, 2011[33]	Case report	1	HCQ	Taiwan	psychosis
Muthukrishnan 2011[34]	Case report	1	HCQ	USA	Cardiomyopathy
Skare 2011[35]	Case series	209 (127 SLE)	HCQ+CQ	Brazil	159 of 209 (76%) had cutaneous findings. Xerosis, followed by skin hyperpigmentation and pruritus; no significant difference found in type of AM, treatment duration and the disease (SLE vs RA) except hair discoloration was more prevalent in SLE
Wolfe 2010[36]	Retrospective Cohort	3995 SLE+RA	HCQ	USA	Retinal toxicity;10 of 84 patients who had eye examinations had definite/probable toxicity and 13 had possible toxicity. The risk of toxicity was low in the initial 7 years of exposure, and was approximately 5 times greater after 7 years of usage (or 1,000 gm total exposure).
Fleury 2009[37]	Case report	1	HCQ	France	Complete ageusia developed shortly after tx started, resolved after discontinued
Lateef 2009[38]	Case report	1	HCQ	Chinese	Acute generalized exanthematous pustulosis (AGEP) and toxic epidermal necrolysis (TEN)
Manohar 2009[39]	Case report	1	HCQ	USA	Restrictive cardiopyopathy- improved after d/c
Collins 2008[40]	Case report	1	CQ	USA	psychosis
Puri 2008[41]	Case report	2 (1 SLE)	HCQ	USA	Hyperpigmented temple
Costedoat-Chalumeau 2007[42]	Cross sectional	85 CTD (70 SLE)	HCQ	France	The rate of heart conduction disorders was similar to what is expected in the general population
Fererras 2007[43]	Case report	2	CQ	Spanish	Toxic retinopathy in both cases
Muslimani 2007[44]	Case report	4 (2 SLE)	HCQ	USA	Myelodysplastic syndrome
Stas 2007[45]	Case report	1	CQ	Belgium	polymorphic ventricular tachycardia, long QT interval and conduction disorders

HCQ=Hydroxychloquine; CQ=Chloroquine; AM= Antimalarials;

APPENDIX 4. Overview of included studies- Effect on fetus

Author/year	Type of study	N	AM	Country/ cohort	AM effect
Izmirly 2012[46]	Historical cohort	257 pregnancies	HCQ	USA, France, UK	↓recurrence of anti Ro/La associated NL† in mothers with history of cardiac-NL, positive antiRo/La; OR 0.23; 95%CI, 0.06 – 0.92; p=0.037
Renault 2009[47]	Case series	21 infants	HCQ	France	Abnormal electroretinogram (ERG) in 6 and delayed visual evoked potentials (VEP) in 4

†NL: Neonatal Lupus; HCQ=Hydroxychloquine; CQ=Chloroquine; AM= Antimalarials;

APPENDIX 5. References for Appendices 1–4.

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