A new role for antimalarials in systemic lupus erythematosus treatment

Antimalarials (AMs) are old drugs in the treatment of connective tissue diseases, especially rheumatoid arthritis and systemic lupus erythematosus (SLE). The clinical context of the use of AMs in SLE, however, has started to change in the last years. The traditional role of AMs as drugs used to treat the mild manifestations of the disease, such as skin involvement and joint pains, is currently evolving. Studies have demonstrated that these are drugs with potential beneficial effects in preventing most of other more severe manifestations and complications in SLE patients. However, some of these effects have been only hypothesized, and are yet to be confirmed in further studies. Thus, we will review the current situation regarding different clinical applications of AMs in patients with SLE.

KEYWORDS: antiphospholipid syndrome ■ chloroquine ■ hydroxychloroquine ■ pregnancy ■ prognosois ■ survival ■ systemic lupus erythematosus ■ thrombosis

Jose-Luis Ayensa[1,2], Munther Khamashta[2] & Guillermo Ruiz-Irastorza[†1]

[1]Service of Internal Medicine, Hospital de Cruces, University of the Basque Country, 48903 Bizkaia, Spain
[2]Lupus Research Unit, The Rayne Institute, St Thomas' Hospital, King's College, London, UK
[†]Author for correspondence:
Tel.: +34 946 006 348
Fax: +34 946 006 617
r.irastorza@euskalnet.net

Antimalarials (AMs) are among the oldest drugs used to treat human disease. Their widespread use in connective tissue disorders started decades ago, particularly after World War II, when thousands of Anglo–American soldiers in the Pacific front received prophylaxis against malaria. It was observed that rheumatic symptoms improved in patients treated with quinine or synthetic antimalarials such as quinacrine. Such observations opened the door for regular treatment of patients with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) with drugs synthesized posteriorly such as chloroquine (CQ) and hydroxychloroquine (HCQ) [1,2]. Since then, AM drugs have been long used for the treatment of SLE and other rheumatic disorders, although their use has been mostly limited to cutaneous and articular manifestations.

In the last few years, however, diverse studies have pointed out that these drugs are also useful in preventing and treating patients with more severe forms of the disease. In the era of new and more expensive therapies for the treatment of connective tissue diseases, AMs still remain drugs with extensive potential beneficial effects that need to be explored.

As there is no current recommendation for the use of AMs in patients with SLE and major organ involvement [3], this article will summarize the different studies regarding the beneficial and adverse effects of AMs in SLE. A recent systematic review performed by our group has analyzed the current position of AMs in SLE therapy, and will serve as the basis for this article [4].

Mechanisms of action

The immunomodulatory effects of AMs are not well understood, although they seem to be mediated by several mechanisms. Interference with antigen processing by means of rising lysosomal pH and modulation of immune response, mediated by Toll-like receptor 9, may be important pharmacological actions [5,6]. AMs also seem to inhibit the traffic of nuclear material, preventing the formation of autoantibodies and the activation of plasmacytoid dendritic cells, and through this preventing in that way the overproduction of IFN-α, a hallmark of active lupus [7–10]. Of note, 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 [5].

Clinical effects of antimalarials
■ Antimalarials & disease activity

As the treatment of SLE has improved in past decades, the mortality and morbidity of the disease has decreased dramatically. Nevertheless, SLE still has the potential to behave aggressively, leading to end-stage organ disease an even death. In these cases of severe disease flare, AMs are often forgotten, as physicians tend to use them only when SLE activity is limited to skin and joints. This attitude is starting to change as diverse studies are showing the benefits of AM use in severe forms of the disease.

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There is high-quality evidence that AMs reduce SLE activity in both pregnant and non-pregnant patients (Table 1) [4,11–23]. All of the studies focused on this issue, regardless of the definition of lupus activity used and consistently demonstrated a significant reduction in activity. Moreover, three studies demonstrated a significant reduction in corticosteroid dose allowed by AMs (steroid-sparing) [12,14,17]. While the capacity of AMs to maintain disease remission is clear, the effect on severe flares and lupus nephritis is not so well established. In randomized controlled trials and prospective cohorts, the benefit has been of borderline statistical significance while in retrospective observational studies statistically significant results have been achieved [19–23]. However, a recent study by Pons-Estel *et al.* within a prospective cohort with active lupus nephritis from the multiethnic Lupus in Minority Populations: Nature Versus Nurture (LUMINA) group found that HCQ was associated with a longer time to the occurrence of renal damage, even if proteinuria was omitted from the end point [22]. Therefore, these data support continuing the use of AMs also in severe flares of SLE.

Table 1. Antimalarials and lupus activity.

Study (year)	Type of study	n	AM	Main outcomes	AM effect	Ref.
Canadian Group (1991)	RCT	25 HCQ 22 PL	HCQ	SLE flare (ACR manifestations) Severe flare Prednisone dose	Lower rate of SLE flare, lower rate of severe flare, no difference in dose of prednisone	[11]
Williams *et al.* (1994)	RCT	40 HCQ 31 PL	HCQ	Painful/swollen joints Grip strength Self-assessed score of severity of joint pain	Lower self-assessed severity of joint pain	[13]
Meinao *et al.* (1996)	RCT	11 CQ 12 Pl	CQ	SLE flare (SLEDAI) Prednisone dose	Lower rate of SLE flare Higher rate of prednisone reduction	[12]
Tsakonas *et al.* (1998)	Retrospective data of extended RCT	25 HCQ 22 PL	HCQ	Time to develop a major flare	Lower rate of major flare	[21]
Levy *et al.* (2001)	RCT	10 HCQ 10 PL	HCQ	SLE activity (SLEPDAI) during pregnancy Prednisone dose	Improvement in SLEPDAI score only in patients on HCQ and lower prednisone dose at delivery (p < 0.05)	[14]
Cortes-Hernandez *et al.* (2002)	Prospective cohort	60	CQ	SLE flares (SLEDAI) during pregnancy	CQ discontinuation increased flares	[18]
Wozniacka *et al.* (2006)	Prospective cohort	25	CQ	Change in SLAM score	Higher reduction in SLAM score	[15]
Costedoat *et al.* (2006)	Prospective cohort	120	HCQ	SLE flare (SLEDAI) Serum levels of HCQ	Lower HCQ serum levels in patients with flare	[16]
Kasitanon *et al.* (2006)	Retrospective cohort	11 HCQ 18 no HCQ	HCQ	Remission in membranous lupus nephritis treated with MMF	Higher rate of membranous LN remission	[20]
Barber *et al.* (2006)	Retrospective cohort	35	HCQ	Sustained remission of lupus nephritis (≥ 3 years)	More patients on sustained remission on HCQ	[19]
Clowse *et al.* (2006)	Prospective cohort	56 HCQ 38 HCQ previous to pregnancy 163 no HCQ	HCQ	SLE activity (PGA, SLEDAI) during pregnancy Prednisone use during pregnancy	Women stopping HCQ higher lupus activity than those never treated and those taking HCQ. ↓ Flare rate, ↓ maximum SLEDAI , ↓ maximum prednisone dose	[17]
Shinjo (2009)	Prospective cohort	57	CQ	HCQ suspension and SLE status in the elderly	Disease remission associated with long term CQ usage	[23]
Pons-Estel *et al.* (2009)	Prospective cohort	203	HCQ	SDI renal damage HCQ Use	Higher dose of HCQ in patients without renal damage Longer time to occurrence of renal damage even if proteinuria omitted from end point	[22]

AM: Antimalarial; CQ: Chloroquine; HCQ: Hydroxychloroquine; LN: Lupus nephritis; MMF: Mycophenolate mofetil; PGA: Physician global assessment; PL: Placebo; RCT: Randomized controlled trial; SDI: SLICC/American College of Rheumatology damage index; SLAM: Systemic lupus activity measurement; SLE: Systemic lupus erythematosus; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SLEPDAI: Systemic Lupus Erythematosus in Pregnancy Disease Activity Index.

Study (year)	Study type	n	HCQ/CQ	Main outcome	AM effect	Ref.
Wallace et al. (1987)	Observational cohort	92	HCQ ever	Thrombosis	Patients treated with HCQ had less thrombosis	[33]
Erkan et al. (2002)	Cross-sectional	58†	HCQ prior to event	Thrombosis	Prior treatment with HCQ more frequent in patients without thrombosis	[36]
Toloza et al. (2004)	Observational cohort	446	HCQ ever	Arterial thrombosis	No effect	[32]
Mok et al. (2005)	Observational cohort	625	HCQ ever	Thrombosis	No significant results	[29]
Ho et al. (2005)	Observational cohort	442	HCQ prior to event	Thrombosis	Less thrombosis	[34]
de Leeuw et al. (2006)	Cross-sectional	72	HCQ ever	CV disease	Patients with CV disease less and lower cumulative dose of HCQ (differences not significant)	[36]
Ruiz-Irastorza et al. (2006)	Observational cohort	232	AM at the time of event	Thrombosis	Less thrombosis	[35]
Mok et al. (2007)	Retrospective cohort	SLE: 162 GN: 181	HCQ > 3 month ever	Arterial thrombosis	No significant results	[38]
Kaiser et al. (2008)	Retrospective cohort	1930	HCQ ever	Thrombosis	Treatment with HCQ protective for thrombosis	[28]
Tektonidou et al. (2009)	Retrospective cohort	288	HCQ ever	Thrombosis	Treatment with HCQ protective for thrombosis in both patients with and without aPL antibodies	[25]

Table 2. Effects of antimalarials on thrombosis.

†This study included 133 patients with antiphospholipid antibodies, of whom 58 had SLE. The results were obtained for the whole group of patients.
AM: Antimalarial; aPL: Antiphospholipid antibodies; CQ: Chloroquine; CV: Cardiovascular; GN: Primary glomerulonephritis; HCQ: Hydroxychloroquine; SLE: Systemic lupus erythematosus.

■ Antimalarials & thrombosis

Thrombosis is a major cause of concern in patients with SLE, occurring with greater frequency and at a younger age than in the general population [24]. Although several risk factors have been identified [25], their relative weight in causing thrombotic events is not yet clear. Antiphospholipid antibodies (aPL) such as anticardiolipin antibodies (aCL), lupus anticoagulant and anti-β2-glycoprotein I antibodies (anti-β2GPI), are detected in approximately one-third of SLE patients and have been associated with an increased risk of both arterial and venous thrombosis [25–28]. Lupus anticoagulant is the most powerful predictor of thrombosis among the different aPL in patients with SLE [25]. Ethnicity may have a role too, as some studies have pointed out that Asian (–American) and African–American patients could have a lower risk for venous thrombosis [28,29]. The development of full-blown APS with thrombosis is a clear adverse factor for survival in patients with lupus [27].

The effect of AMs in preventing thrombotic events has been intuited by British orthopedic surgeons since the early 1970s. They used HCQ for preventing episodes of deep venous thrombosis and pulmonary emboli in patients recovering from total hip replacement, with seemingly beneficial results [30,31].

The magnitude of this effect has been thoroughly studied over the past few years [28,29,32–38]. These studies mainly showed that HCQ/CQ has either a protective [27,28,33–36], or borderline protective [29,37] effect against thrombosis (TABLE 2). Only one study in which patients with both SLE-related

and non-SLE related glomerulonephritis were mixed-up, failed to show any beneficial effect (most likely owing to a confounding by indication bias) [38]. It is suggested that a dose effect is present [25], however, further studies will be needed to confirm the magnitude of this effect. Likewise, there are insufficient data to address whether the antithrombotic effect is present on both arterial and venous events [27,28,34–36].

More recently, Tektonidou *et al.* have published the results of a study of lupus patients with aPL antibodies with or without episodes of thrombosis. The results demonstrated that exposure to HCQ played a protective role in both aPL-positive and aPL-negative groups [25]. Another study by Kaiser *et al.* in a large multi-ethnical cohort of 1930 SLE subjects also showed the protective effect of HCQ against thrombosis [28]. Very recently, a study within the Toronto Lupus Cohort [39], has confirmed the antithrombotic effects of AMs using a case-control design, matching patients by age, time to follow-up and Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score. Of note, a similar protective effect has been shown for both arterial (OR: 0.34; 95% CI: 0.12–0.99) and venous events (OR: 0.26; 95% CI: 0.07–1.02).

■ Antimalarials & cardiovascular disease

With the improvement of immunosuppressive therapy and the subsequent better control of lupus, diminishing the impact of infections and active disease on the prognosis, atherosclerotic disease is now one of the major concerns in patients with SLE. Studies are still trying to identify which are the risk factors, apart from traditional ones such as diabetes or hypertension, that make SLE patients prone to early cardiovascular disease.

The effect of CQ on 2,3-oxidosqualene-lanesterol cyclase and the stimulation of low-density lipoprotein receptor activity in fibroblasts has been linked with the inhibition of cholesterol synthesis. This mechanism could support an effect of AM in the reduction of lipid levels [40,41].

In 1993, Hodis *et al.* carried out a cross-sectional study that suggested that patients receiving HCQ had lower levels of triglycerides (TG), very-low-density lipoprotein cholesterol and apoCIII [42]. Later studies tried to confirm the beneficial effect of AMs in lowering cholesterol and TG, with diverse conclusions, showing a trend towards significant results [42–52]. All but two studies found significant reduction in serum levels of lipid parameters in patients receiving AM [47,50]. The largest study by Petri *et al.* [49], using multivariate analysis, concluded that HCQ lowered TG levels.

The relationship between lipid profile and AMs in patients who are administered corticosteroids has been analyzed in three studies, finding significant reduction of TC, very-low-density lipoprotein cholesterol, low-density lipoprotein cholesterol and TG levels, and also a significant increase in HDLc levels, when compared with patients receiving corticosteroids alone [45,47,48].

The relationship between AMs and metabolic syndrome has been recently studied. Although the study by Chung *et al.* showed no influence of HCQ in the presence of metabolic syndrome [51], two recent studies by Bellomio *et al.* [52] and Sabio *et al.* [53] have shown that patients with less intake of HCQ had a higher prevalence of metabolic syndrome in both Argentinean and Spanish cohorts, respectively.

Patients with SLE also have a tendency to develop atherosclerotic disease earlier in life compared with the normal population. Of the eight studies that analyze the effect of AM on atherosclerosis (defined as the presence of carotid plaque and/or abnormal intima/media index by carotid ultrasound, of coronary calcifications by CT scan or by studies of vascular elasticity) [54–61], only the study by Tanay *et al.* found significant benefits among patients treated with HCQ as compared with untreated patients or those receiving corticosteroids alone [61]. This was the only study specifically designed to analyze the relationship between HCQ and atherosclerosis.

A recent study from Pons-Estel *et al.* with 637 SLE patients from the LUMINA cohort attempted to determine predictors of cardiovascular damage, defined as angina or coronary artery by-pass surgery, myocardial infarction and/or congestive heart failure [62]. Whilst traditional risk factors (age, gender) and disease related factors (C-reactive protein levels, Systemic Lupus International Collaborating Clinics [SLICC]/ American College of Rheumatology [ACR] damage index [SDI] at baseline) appeared to be important contributors to cardiovascular damage, no significant relationship with the use of HCQ was found.

Data from studies performed in patients with other autoimmune disorders suggest an improvement in glucose metabolism, with a better control of type 2 diabetes mellitus and also preventing the development of this illness [63]. The study by Wasko *et al.* in 2007 showed that, among patients with RA, HCQ was associated with a lower risk of developing diabetes (adjusted HR:

Table 3. Effects of antimalarials on irreversible organ damage.						
Study (year)	Study type	n	HCQ/CQ	Main outcome	AM effect	Ref.
Molad et al. (2002)	Prospective cohort	151	HCQ	Damage-free survival SDI at last visit	Higher damage-free survival HCQ independent relation with lower SDI	[77]
Fessler et al. (2005)	Prospective cohort with propensity score analysis	518	HCQ	Time to new damage	Borderline results Significant results in patients with no damage at entry	[72]
Pons-Estel et al. (2009)	Prospective cohort with active lupus nephritis	203	HCQ	Renal damage	Higher dose of HCQ in patients without renal damage Longer time to occurrence of renal damage even if proteinuria omitted from end point	[22]
AM: Antimalarial; HCQ: Hydroxychloroquine; SDI: SLICC/American College of Rheumatology damage index.						

0.62; 95% CI: 0.42–0.92) [64]. In fact, patients with a history of 4 or more years of HCQ use had an adjusted relative risk of developing diabetes of only 0.23 (95% CI: 0.11–0.50). This has yet to be confirmed in studies designed to that effect in patients with SLE.

■ Antimalarials & bone metabolism
Prophylaxis of osteoporosis is nowadays an important goal in the treatment of SLE. Some treatments used in these patients tend to accelerate bone loss (e.g., corticosteroids, low-molecular-weight heparins in patients with aPL antibodies).

Two studies were designed to analyze the effect of HCQ on bone mineral density (BMD) in a small cohorts of patients with SLE [65,66]. The study by Mok et al. showed that current/past use of HCQ and cumulative HCQ dose were associated with higher mean BMD of the spine [65]. The study by Lakshminarayanan et al. pointed out that the length of HCQ therapy correlated positively with the mean BMD of the hip and negatively with osteopenia/osteonecrosis of the spine [66].

Similarly, two case-control studies by Calvo-Alen et al. [67] and Prasad et al. [68] analyzed the relationship between HCQ exposure and osteonecrosis, finding a lower exposure time in patients with osteonecrosis (no significant difference in the multivariate model) and no differences, respectively.

The relationship between HCQ and $1–25 (OH)_2$ vitamin D was also analyzed by Huisman et al. [69] in a cross-sectional study of a small cohort of patients with either SLE or fibromyalgia. They found lower $1–25 (OH)_2$ D levels in patients with lupus treated with HCQ. However, circulating 25 (OH) D levels did not differ between treated and untreated patients. Therefore, the effect of AMs on vitamin D levels is not clear, and it could be even argued that AMs may spuriously increase 25 (OH) D levels,

at the expense of reducing the metabolically active form, $1–25 (OH)_2$ D. However, we could also postulate that the role of AMs as corticoid-sparing agents may have an important impact on bone mass preservation in lupus patients.

■ Antimalarials & end-organ disease
Being a chronic disease that usually becomes milder in later stages of life, SLE causes, a high degree of organ damage that accrues throughout the years. The SLICC group developed a clinical index of chronic damage [70,71], including features related to disease activity (e.g., skin scarring and proteinuria) as well as features that could be more commonly associated with drugs used to treat lupus (e.g., osteoporosis and diabetes). This index, known as the SDI, has shown to be reliable for measuring irreversible damage accrual over time, with prognostic implications in terms of morbidity and mortality [72,73].

Three studies have addressed the relationship between damage accrual, using the SDI, and AM treatment (TABLE 3). The first study, by Molad et al. [74], was performed in a cohort of mostly Israeli patients, showing an inverse and independent relationship between treatment with HCQ and SDI values after 45 months follow-up. A higher damage-free survival was noted in patients treated with HCQ that in nontreated patients. In a second study by Fessler et al. [75] with 518 patient from the LUMINA cohort, HCQ treatment taken at the time of enrolling the cohort was shown to be protective against damage accrual. This effect of HCQ treatment on SDI was adjusted using the propensity score [76], and was especially relevant in those patients with no damage at the time of entering the study [75]. More recently, Pons-Estel et al. have demonstrated the effect of AM in preventing renal damage in a prospective cohort with active lupus nephritis [22].

Table 4. Effects of antimalarials on survival.						
Study (year)	Study type	n	HCQ/CQ	Main outcome	AM effect	Ref.
Hernandez-Cruz et al. (2001)	Case-control	152	CQ	Survival	Higher dose of CQ in alive patients CQ nonsignificant predictor of survival in logistic regression	[77]
Ruiz-Irastorza et al. (2006)	Prospective cohort with propensity score analysis	232	HCQ/CQ	Survival Causes of death	Prolonged survival in AM group No cardiovascular deaths in AM group vs seven in the untreated group	[35]
Alarcon et al. (2007)	Case–control with propensity score analysis	244	HCQ	Survival	Prolonged survival in AM group	[78]
AM: Antimalarial; CQ: Chloroquine; HCQ: Hydroxychloroquine.						

■ **Antimalarials & survival**

Survival in SLE has improved dramatically over the last decades. Currently, 10-year survival rates were approaching 90% in many studies, while the 5-year survival rate was approximately 50% in 1955 [77–79]. In spite of this, mortality rates for patients with SLE are still three- to five-times higher than those of the general population. Several studies have been developed to try to measure the effect of AM in improving survival in patients with SLE (TABLE 4).

The first study in which the effect of AMs in survival was investigated involved selecting autopsies and hospital registers of SLE patients from Mexico City (Mexico) [80]. There was significant evidence of a lower dose of CQ in deceased than in living patients, although this study is likely to have a "confounding by indication" bias and is clearly limited by the retrospective acquisition of the data.

Two recent studies have been specifically designed to address the influence of AMs in the long-term survival of patients with SLE. The first of these studies was performed in the Lupus–Cruces cohort from the Basque Country, Spain [35], and one using the multiethnic prospective LUMINA cohort [81]. Both studies used the propensity score to overcome the potential confounding by indication bias. A consistent significant inverse relationship between treatment with AMs and mortality was found, with a reduction of mortality higher than 50% in both studies. This was true despite the racial diversities included in the LUMINA group (Hispanics, African–Americans and Caucasians).

These results have been confirmed by a large study of the Grupo Latino Americano de Estudio de Lupus (GLADEL), which analyzed the survival factors in a cohort of 1480 patients with lupus [82]. The study showed a decreased mortality in patients taking AMs, with a clear dose effects, the lowest mortality was seen in patients taking AMs for more than 2 years.

In a retrospective analysis of a cohort of patients with biopsy-proven lupus nephritis, Sisó et al. also found a decreased mortality rate among previous AM users [83].

Despite the obvious limitations of a non-randomized design and the division of patients between ever and never treated, the magnitude of the effect after the propensity score adjustment is unlikely to be fully explained by unidentified confounders. In addition, a dose effect is suggested by the GLADEL study. Thus, a clinically relevant effect of AM in reducing long-term mortality of patients with SLE is strongly supported by these results. This effect is particularly important, as no similar long-term benefits have been demonstrated for other drugs used to treat SLE.

Antimalarials in pregnancy

Since the majority of patients suffering from SLE are women of childbearing age, pregnancy is likely to become an issue at some point during the course of the disease. Currently, the possibilities of a successful pregnancy are high in women with lupus. Careful combined medical–obstetric management monitoring is essential in order to assure the best care. One of the important points regarding pregnancy, is to choose those drugs that can help to control SLE with a minimum risk of toxicity for the baby. Along with prednisone, azathioprine and low-dose aspirin, HCQ is one of the drugs that can be considered safe during pregnancy [4].

Table 5. Antimalarials and fetal toxicity.						
Study (year)	**Study type**	**n**	**Antimalarial**	**Main outcome**	**Result**	**Ref.**
Levy et al. (1991)	Retrospective cohort	14 SLE 3 RA 4 malaria	HCQ (n = 4) CQ (n = 17)	Malformations Eye abnormalities Hearing impairment	14 live births No toxicity	[79]
Parke et al. (1996)	Prospective cohort	9	HCQ	Malformations Clinical exam	No toxicity	[80]
Buchanan et al. (1996)	Retrospective cohort	36 HCQ 53 control	HCQ	Prematurity Weight at birth IUGR Fetal distress Malformations Visual disturbance	No difference with controls	[81]
Kilnger et al. (2001)	Cross-sectional	21 (SLE + RA)	HCQ (n = 14) CQ (n = 7)	Ophthalmologic examination at mean 2.8 years of age	No toxicity	[82]
Levy et al. (2001)	RCT	10 HCQ 10 PL	HCQ	Clinical exam Auditory exam Ocular exam (at 1.5–3 years of age)	No toxicity No difference with controls	[14]
Costedoat et al. (2003)	Prospective cohort	133 HCQ 53 control	HCQ	Fetal death Premature birth Weight Malformations Electrocardiogram Clinical exam at 12–108 months	No difference with controls No toxicity	[83]
Borba et al. (2004)	Cross-sectional	19 CQ 10 control	CQ	Pure tone audiometry (age > 4 years of age)	No difference with controls No toxicity	[84]
Cimaz et al. (2004)	Prospective cohort	6	HCQ	Malformations Weight Electroretinogram	No toxicity	[86]
Motta et al. (2005)	Prospective cohort	21 SLE 6 UCTD 4 MCTD 3 SACLE 3 PAPS 2 RA 1 SS	HCQ	Prematurity Malformations Visual function and neurodevelopmental outcome at 1 year of age (n = 24)	No toxicity	[85]
Clowse et al. (2006)	Prospective cohort	56 HCQ 38 HCQ previous to pregnancy 163 no HCQ	HCQ	Malformations Visual or hearing impairment	No difference with controls No toxicity	[17]
Sperber et al. (2009)	Meta-analysis	4 studies: 3 cohort and 1 case control	HCQ	Malformations Fetal death Prematurity	No toxicity	[87]

AM: Antimalarial; CQ: Chloroquine; HCQ: Hydroxychloroquine; IUGR: Intrauterine growth restriction; MA: Malaria; MCTD: Mixed connective tissue disease; PAPS: Primary antiphospholipid syndrome; RA: Rheumatoid arthritis; RCT: Randomized controlled trial; SACLE: Subacute cutaneous lupus erythematosus; SLE: Systemic lupus erythematosus; SS: Sjögren's syndrome; UCTD: Undifferentiated connective tissue disease.

All of the studies that have analyzed the effect of AMs on the fetus concluded that there is no higher incidence of congenital malformations when compared with unexposed babies (Table 5). In addition, no ocular, auditory or neurological toxicity has been reported [14,17,84–91]. Recently, a meta-analysis by Sperber et al. [92] studying the effects of HCQ in pregnant patients with autoimmune diseases also confirmed that there was not a higher incidence of congenital defects, spontaneous abortions, fetal deaths or prematurity in women treated with HCQ. Given the safer profile and the larger experience in pregnant SLE women with HCQ as compared with CQ, the former is recommended. Both are also safe during nursing [93].

Regarding the effects on SLE, data have been specifically obtained from pregnant women that confirm a higher risk of lupus flares if AMs are withdrawn during pregnancy [14,17,18]. Given the

adverse prognostic consequences of lupus activity on both the mother and the baby, the use of AMs, mainly HCQ, is also highly encouraged during pregnancy.

Miscellanea

Infections are among the most feared complications of SLE therapy, being one of the leading causes of death. However, AMs provide effective immunomodulation without immunosuppression [5], in fact, they are antimicrobial agents with a wide spectrum against parasites as well as bacterial and even viral agents [94]. Thus, the possible role of AMs in preventing the development of infections would make sense, but it has not been analyzed until recently. Two studies by Siso *et al.* [83] and Butnik *et al.* [95] observed a decreased frequency of infections in patients taking AMs that was attributed, however, to less severe SLE manifestations in this group. Ruiz-Irastorza *et al.* recently designed a nested case-control study to analyze the diverse predictors of major infections within a prospective cohort of 289 patients with SLE [96]. Lung disease (associated with pneumonia) and treatment with prednisone and AMs were the independent predictors: whilst prednisone increased the risk of infection, AMs had a protective effect.

Another potential effect of AMs, which can be inferred from their effect on lupus activity, could be preventing or delaying the development of full-blown lupus. James *et al.* designed a study that analyzed the effect of HCQ in delaying the fulfilment of ACR criteria for SLE in patients with lupus-like disease [97]. HCQ showed a delaying effect in completing the classification criteria, with patients being less likely to present with proteinuria, leukopenia or lymphopenia.

The development of malignancies is one of the complications that causes major concern in patients with SLE. Recent large observational studies have found that patients with lupus have a higher probability of developing cancer than the normal population, the specially non-Hodgkin lymphoma (incidence ratio of 2.75 and 3.64, respectively) [98]. AMs have the potential effects of stabilizing DNA and inhibiting telomerase. There is only one study that has attempted to analyze the effect of AMs on the risk of developing cancer. Ruiz-Irastorza *et al.*, in a study within a prospective cohort of SLE patients, suggested that AMs may have a protective effect on the risk of developing cancer [99].

Toxicity of antimalarials

Traditionally, AMs have been considered relatively safe drugs. After widespread use, the frequency of reported adverse effects has been low. The major cause of concern for physicians is ocular toxicity due to AM accumulation in the retina. The most severe form of retinopathy is maculopathy (bull's eye lesion), which can progress even after AM withdrawal and even lead to blindness. AMs can also cause keratopathy, ciliary body involvement and lens opacities, however these are usually of a milder nature.

The first reports addressing retinal toxicity due to AMs appeared in the 1950s. In 1959, Hobbs established a definite link between long-term use of CQ and subsequent development of retinal toxicity, with cases of retinal toxicity having been subsequently reported [100–110]. A retrospective study performed in 1982 by Frankel *et al.* in a cohort of patients taking HCQ failed to show any case of ocular toxicity [111]. Subsequent studies, some of which included diseases other than SLE [105,112–115], have been analyzed in a recent systematic review. Among a cohort of 2043 patients treated with HCQ for more than 10 years, only two (0.1%) developed definite retinal toxicity, versus 16 patients (2.5%) in the pooled group of 647 patients from the studies in which CQ was used. When adding probable cases of retinal toxicity the trend was similar, showing 17 patients (2.6%) for CQ use and six patients (0.3%) for HCQ use.

Thus, it could be concluded that whilst retinal toxicity is a dreadful complication in patients receiving AM, it is actually rare, especially in people treated with HCQ. Still, labeling a patient as having definite data of retinopathy is not easy, as many of the patients reported do not fulfil the high-risk criteria proposed by the American College of Ophthalmology [116]. Therefore, in the setting of SLE, the recommendations of Marmor *et al.* [116] of annual eye screening seem reasonable. As suggested by Alarcón, a low HCQ dosage, short duration of therapy or young age do not preclude the occurrence of AM retinopathy in SLE patients [117]. However, even patients at high risk, should be considered at very low absolute likelihood of developing retinopathy, especially when using HCQ.

Other reported adverse effects when using AMs are mainly gastrointestinal and cutaneous and usually mild [103,112,118,119]. The study by Aviña-Zubieta *et al.* [112] is the only one study that compared HCQ and CQ and demonstrated a higher frequency of adverse effects in patients receiving CQ (28.4 vs 14.7% in patients receiving

HCQ) and also that patients on HCQ were less likely to abandon the follow-up due to drug toxicity. Cardiotoxicity has also been reported in 14 case reports [102,120–128], however, two studies that attempted to evaluate this condition [120,129] have failed to demonstrate clinically demonstrated relevant cardiac toxicity. Other much less frequent side effects include myopathy, usually related to CQ treatment [4], hypoglycemia, which could be an issue in patients treated with anti-diabetic drugs [63], ototoxicity, fulminat hepatic failure and bone marrow toxicity [4]. However, they are seldom an issue in clinical practice.

In general, doses below 6.5 mg/kg/day of HCQ and 3 mg/kg/day of CQ are well tolerated [4].

Relation between blood levels & efficacy of AM

It is important to take into account that blood levels of AMs can influence their clinical effects. Costedoat *et al.* showed that low whole-blood HCQ concentrations were associated with a statistically significant higher SLE activity [16]. Blood HCQ concentrations were a strong predictor of disease exacerbartion (OR: 0.4; 95% CI: 0.18–0.85).

It has been suggested that smoking could interfere with the drug metabolism as cigarette smoking is a potent inductor of cytochrome P450 and AMs are partly metabolized by this enzyme system. A study conducted by Jewell *et al.* in a small cohort of cutaneous SLE patients showed that the response rate to AMs was superior in non-smokers (90%) than in smokers (40%) [130]. Leroux *et al.* studied the relationship between HCQ and desethylchloroquine, a derivate of the drug, and cigarette smoking. They found no differences in plasma levels of these metabolites when analyzing the data between smokers and non-smokers [131].

Conclusion

It can be concluded that there is high evidence that AMs increase long-term survival in SLE patients [4]. The data also show protection against irreversible organ damage, bone mass loss and thrombosis, all with a moderate grade of evidence [4]. There is also weaker evidence of the effect AMs have on lowering lipid levels and protecting against atherosclerosis and severe lupus. Protecting the development of full-blown SLE, lowering the incidence of cancer in SLE patients and regulating vitamin D levels are currently discussed in single studies however that data will need further confirmation.

Improvement in glucose metabolism and type 2 diabetes mellitus has been suggested in patients with RA and studies to prove this benefit in

Table 6. Effects of antimalarials in systemic lupus erythematosus patients graded according to the quality of evidence.	
Quality of evidence	**AM**
High	
- Reduction of SLE activity (also in pregnancy)	CQ/HCQ
- Reduction of mortality	CQ/HCQ
Moderate	
- Increase in BMD	HCQ
- Protective effect on thrombotic events	CQ/HCQ
- Protective effect on irreversible organ damage	HCQ
Low	
- Reduction of severe flares	HCQ
- Adjuvant effect for achieving LN remission	HCQ
- Beneficial effect on serum lipid levels	CQ/HCQ
- Protective effect on osteonecrosis	HCQ
- Delaying the evolution to SLE	HCQ
- Protective effect on cancer	CQ/HCQ
Very low	
- Reduction of 1–25 $(OH)_2$ vitamin D levels	HCQ
- Reduction of atherosclerosis	CQ/HCQ
AM: Antimalarial; BMD: Bone mineral density; CQ: Chloroquine; HCQ: Hydroxychloroquine; LN: Lupus nephritis; SLE: Systemic lupus erythematosus. *Data according to* [4].	

patients with SLE will be needed. The quality of evidence of the effects of AMs on different aspects of SLE, as reported in [4], is summarized in TABLE 6.

In addition to these beneficial effects, it can be said that toxicity due to AMs is infrequent, usually mild, frequently reversible and rarely a reason for withdrawing the treatment. There is also high levels of evidence that AMs decrease lupus activity in pregnant patients without harming the baby. These data on efficacy and safety are more solid for HCQ than for CQ, which has a more toxic profile and has been less frequently studied.

The different role that HCQ and CQ may have is not yet clear. The dose of AMs has not been clearly defined in the variety of studies (it ranges from 250–500 mg for CQ and 100–400 mg for HCQ). The lowest effective dose of both of these drugs is yet to be confirmed in subsequent trials. Our practice is using 200 mg/day with eventual dosing of 400 mg/day in individual cases. Due to the less favorable safety profile, CQ is almost never used.

The evidence defining the role of AM in SLE is evolving rapidly. Today, taking into account the clinical data already available, these drugs, particularly HCQ, should be considered the cornerstone for the long-term treatment of SLE. Unfortunately, AMs are used only in a subset of SLE patients, usually those with milder disease. Results from a study by Schmajuk *et al.* in a cohort of 881 SLE patients and 3095 person-years of follow-up show that the prevalence of HCQ use was only 55%. The strongest predictors for not being treated with HCQ were the physician speciality

(non-rheumatologist) and longer disease duration, reflecting the trend to stop HCQ use after longstanding disease remission [132].

This is an important point to highlight: AMs should not be stopped either when SLE is inactive or when additional drugs, such as immunosuppressants, are needed. Although they cannot replace more intensive therapies, AMs play a fundamental adjuvant role in patients with severe disease.

Future perspective

Treatment of SLE has changed over the last 20 years and will further evolve in the coming years. As the tendency is now to use modern and more expensive therapies, drugs such as AM must not be forgotten. Currently, AMs benefits are commonly underestimated in the treatment of SLE, perhaps because they are only seen in their traditional role of treating mild skin and articular manifestations. Every year, data in the medical literature are enhancing the multiple beneficial applications of AM and these must encourage physicians to use these drugs in their SLE patients. In the era of modern immunosuppressants and autoantibodies, there should be room for cheap and safe drugs such as AMs. Taking into account the clinical data already available, these drugs, particularly HCQ, should be considered the basis for the long-term treatment of SLE.

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Executive summary

Antimalarials & disease activity
- There is high evidence of reduction of lupus activity.
- Evidence supporting a reduction of severe flares and an adjuvant effect in achieving lupus nephritis remission is low, although very recent data point in that direction.

Antimalarials & thrombosis
- There is moderate evidence of protection against thrombotic events.
- Data to address whether the protection is similar for both arterial and venous events are insufficient.

Antimalarials & cardiovascular disease
- There is low evidence of a beneficial effect on serum lipid levels.
- Evidence supporting a reduction of atherosclerosis is of very low quality.

Antimalarials & bone metabolism
- There is moderate evidence of increasing bone marrow density in systemic lupus erythematosus (SLE) patients.
- Evidence supporting a protective effect in osteonecrosis is weak.

Antimalarials & end-organ disease
- A protective effect on irreversible organ damage accrual is supported by moderate quality evidence.

Antimalarials & survival
- There is high evidence of a reduction of mortality in SLE patients teated with antimalarials. A dose effect is likely in the light of recent research.

Antimalarials & pregnancy
- There is high evidence of a reduction of lupus activity during pregnancy with virtual absence of fetal toxicity.

Miscellanea
- Individual study data suggest that antimalarials help delay the evolution to SLE and protect against cancer and major infections.

Toxicity of antimalarials
- The adverse effects of antimalaials are usually mild and reversible.
- Retinopathy is a rare complication with hydroxychloroquine; however, it would be prudent to recommend annual eye screening.

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