Long-term use of antimalarial drugs in rheumatic diseases

J.A. Jover[1], L. Leon[1,2], E. Pato[1], E. Loza[3], Z. Rosales[1], M.A. Matias[4], R. Mendez-Fernandez[5], D. Díaz-Valle[5], J.M. Benitez-del-Castillo[5], L. Abasolo[1]

[1]Rheumatology Unit, Hospital Clinico San Carlos, Madrid; [2]Camilo Jose Cela University, Madrid; [3]Research Unit, Fundación Española de Reumatología, Madrid, Spain; [4]Rheumatology Unit, Hospital Infanta Leonor, Madrid; [5]Ophtalmology Unit, Hospital Clinico San Carlos, Madrid, Spain.

Abstract

Objectives

To evaluate long-term use of antimalarial drugs and to analyse all causes of discontinuation.

Methods

This is a retrospective study of a cohort of rheumatic diseases patients on antimalarials, during a maximum period of 17.5 years. Case was defined as antimalarial treatment discontinuation due to: a) lack of efficacy, b) adverse events, and c) other causes. Survival techniques were used to estimate the incidence rate (IR) per 1,000 patient-years with the 95% Confidence Interval (95% CI) of antimalarial treatment discontinuation. Cox regression models were conducted to evaluate possible associated factors to antimalarial discontinuation.

Results

One thousand, two hundred and ninety-one medical records were reviewed, and 778 patients were included. Patients started 869 different courses of treatment, with a total follow-up of 2,263 person-years. The IR of global discontinuation was 204 (95% CI 186–224). Fifty-two per cent of the treatments stopped were related to adverse events, 14% to lack of efficacy; and 34% to other reasons (refusal to take medication, ocular comorbidity, remission, or pregnancy). Adverse events discontinuations were related to non-ophthalmologic reasons in 54.5% (gastrointestinal, neuro-psychiatric, skin problems), and to ophthalmologic adverse events in 45.5%. Nine patients suffered definite presence of antimalarial retinopathy (IR: 3.97 [IC 95%: 2.06–7.62]) and one of them irreversible loss of vision (IR: 0.44 [IC 95%: 0.06–3.12]). Women, increasing age, and chloroquine vs. hydroxychloroquine use, increased the risk of discontinuation due to ophthalmologic adverse events.

Conclusion

Results suggest that antimalarials have a good balance between benefit and risk. However, we noted a number of discontinuations due to both inefficacy and adverse events. The potential for an unusual but serious ophthalmologic toxicity emphasises the importance of close ophthalmologic monitoring.

Key words

rheumatic diseases, antimalarials, long-term use, safety

Juan A. Jover, MD, PhD
Leticia Leon, MS, PhD
Esperanza Pato, MD
Estibaliz Loza, MD
Zulema Rosales, MD
Maria Angeles Matias, MD
Rosalia Mendez-Fernandez, MD
David Díaz-Valle, MD, PhD
Jose M. Benitez-del-Castillo, MD, PhD
Lydia Abasolo, MD, PhD

Please address correspondence to:
Leticia Leon, MS, PhD,
Rheumatology Unit,
Hospital Clinico San Carlos,
Calle Profesor Martin Lagos S/N,
28040 Madrid, Spain.
E-mail: lleon.hcsc@salud.madrid.org

Received on June 6, 2011; accepted in revised form on October 26, 2011.

Funding: This work was partially supported by a grant from the Fondo de Investigaciones Sanitarias of the Spanish Ministry of Health numbers FIS PI08/1205. Included in RETICS Program, RD08/0075 (RIER) from Instituto de Salud Carlos III (ISCIII).

Competing interests: none declared.

Introduction

The antimalarial drugs (AM) chloroquine (CQ) and hydroxychloroquine (HCQ) are commonly used in the treatment of several systemic autoimmune diseases (1-4) including rheumatoid arthritis (RA), systemic lupus herithematosus (SLE) and antiphospholipid syndrome (APS).

AM were introduced throughout the past century, and have been found useful for treating autoimmune diseases either alone or in combination with other drugs (3). We now know that CQ and HCQ may act at several different levels of autoimmune diseases, modifying both immunologic and inflammatory pathways that include the steps involved in the association of antigenic peptides with major histocompatibility complex (MHC)-encoded proteins (5, 6).

It is estimated that more than 50% of patients with RA or SLE will use AM during their disease course (1, 4, 7, 8). Such a widespread use can be explained by their unique combination of wide clinical indication spectrum, good clinical response, and relatively low toxicity potential, in addition to a solid knowledge regarding their mechanism of action.

In fact, AM are usually considered the least toxic of second-line drugs (3, 7, 9-11). Nevertheless, a key issue regarding AM safety is the development of an AM-specific retinal toxicity. This retinal toxicity is probably related to the high AM concentrations reached in the pigmented ocular tissues, which eventually leads to the destruction of rods and cones, with the consequent loss of vision and blindness (12-14). Serious retinal toxicity, which occurs more frequently with CQ than HCQ (14-18), can be prevented with periodic ophthalmologic examinations that detect early, asymptomatic changes that warrant AM discontinuation (14, 17, 19, 20).

Despite their good efficacy-safety profile, observational studies of CQ and HCQ have showed a relatively high discontinuation-rate of these drugs (2, 4, 21, 22). Importantly, the reasons for this apparent discrepancy are not clear.

The aim of our work is to provide new insights into the long-term use of antimalarial drugs, with a special emphasis in the causes of treatment discontinuation, in order to improve the quality of use of two of the most useful drugs in the treatment of rheumatic diseases in real life conditions.

Patients and methods

Setting and practice description

The Rheumatology Service at the Hospital Clínico San Carlos (HCSC) provides specialised rheumatologic care for the 600,000 residents of health district 7 in Madrid, Spain. Patients in our district have direct access to primary care physicians, who refer patients to specialised care when needed. The activity of the Rheumatology Service includes more than 6,500 new and 25,000 successive visits/year. In addition to the clinical visits, patients on second-line drug therapy are included in different follow-up programmes to prevent serious drug toxicities.

Patients receiving antimalarial drugs (AM) are referred to the Ophthalmologic Service from the onset of the treatment. Since 1990 ophthalmologists have followed up each patient at 6-month to one-year intervals, according to a specific protocol developed by both Rheumatology and Ophthalmology Services. Ocular results from every visit have been registered in a standardised form since 1994.

Study design

This is a retrospective observational study based on the review of clinical records. It was conducted in accordance with the Declaration of Helsinki and Good Clinical Practices, and was approved by the HCSC Ethics Committee.

Study subjects

Study subjects met the following inclusion criteria: 1) to have been attended at the Rheumatology Service some time in the period between January 1990 and July 30th 2007; and 2) to have received a prescription for AM (CQ, HCQ). Causes for exclusion were: 1) patients with unavailable medical records, and 2) absence of at least one follow-up visit.

Patients were identified from the following sources: 1) a general Electronic Database of the Rheumatology Service (BDCR, 1990–2004) that includes all

visits and first visit-diagnoses (ICD9 and ICD10) of all patients attended by our Service; 2) from a specific electronic database of the Rheumatology Service of patients with rheumatoid arthritis (OBDAR, 1992–2009) that includes longitudinal comprehensive information regarding treatments, disease activity, adverse events and outcomes; 3) from an Electronic Health Record (Medi-LOG, 2004–2009) that includes comprehensive information regarding diagnoses (ICD9 and ICD10), treatments, disease activity, adverse events and outcomes of all patients routinely attended in our Service; and 4) from the General Information System of our hospital that includes administrative data of patients attended in specialised care, including appointments to the ophthalmology unit where most patients on AM are followed up. After cross-matching the four sources, a list of patients with potential use of AM was obtained. AM use was confirmed by reviewing the medical records.

Variables

A case was defined as antimalarial treatment discontinuation due to: 1) lack of efficacy, 2) AM-related adverse events (AE), and 3) other causes (defined as patient decision, medical decision, non-AM related ocular comorbidity, and miscellaneous). AM-related adverse events were classified into: *a*) non-ophthalmologic adverse events (NOAE) such as digestive, neuro-psychiatric, cardiological, skin, and other ailments; and *b*) ophthalmologic adverse events (OAE). The latter were classified as: b.1) AM-related definitive retinal toxicity (early asymptomatic retinopathy and symptomatic retinopathy), and b.2) AM-related non-retinal toxicity (keratopathy, ciliary body involvement and lens opacities) (14, 17, 19, 20, 23-25).

Other variables analysed were: 1) demographics (age and sex), 2) diagnoses (ICD9 and ICD10), and 3) antimalarial-related including a) type of AM used (HCQ *vs*. CQ), b) number of AM used (defined as treatment with one *versus* both AM at different times during the study period), c) prescription and discontinuation dates, and d) type of discontinuation (temporary or permanent).

Data collection

The review of the medical records from all patients included in the study was performed by a team composed of two staff rheumatologists, two rheumatology residents, and two staff ophthalmologists with experience in ocular manifestations of rheumatic diseases and related treatments.

The different variables and causes of discontinuation were classified by the two residents and the two staff rheumatologists on the basis of the narrative and the data found in the clinical records. In addition, all cases of discontinuation related to AM ocular toxicity were classified following Easterbrook's definition of definitive ocular toxicity related to AM (14, 23, 25). Each case was first reviewed by the two rheumatologists working together and then by two independent ophthalmologists, all of them using the primary data of all ophthalmologic evaluation forms that included the following assessments: visual acuity, colour vision testing (Farnsworth D-15), Amsler grid, visual field testing (Humphrey 10-2 program) (14), and ophthalmologic complete examination (slit lamp examination and fundoscopic examination) (17). When one of the opinions differed, cases were analysed in common and a consensus reached.

Data analysis

Descriptive analyses were performed from the cross-sectional analysis of first visits and the results were compared using the Student's *t*-test or Chi-Square test depending on the type of the variables.

Survival analysis was used to estimate the time elapsed before the occurrence of a case related to the use of antimalarial drugs (multiple-event data, which means that one or more events occur for the same subject), and to estimate the incidence rates for antimalarial treatment discontinuation (for all kinds of events, and especially for those due to lack of efficacy, new ophthalmologic, and non ophthalmologic adverse events). Kaplan-Meier curves were set to account for AM discontinuation. Incidence rates were given per 1,000 patient-years with a 95% of Confidence Interval (95% CI). Time of exposure was the period from the date of each treatment initiation until the occurrence of any of the following ending-points: loss of follow-up due to any cause, AM discontinuation (due to lack of efficacy, adverse events or others), or the end of the follow-up period (27th July 2007).

Cox bivariate and multivariate regression models were conducted to examine risk factors for AM discontinuation. Results were expressed as hazard ratio (HR) and 95% CI. All analyses were performed using Stata 10 statistical software (Stata Corp., College Station, TX, USA). A two-tailed *p*-value under 0.05 was considered to indicate statistical significance.

Results

From the 1,291 patients with potential use of AM, 484 did not meet the inclusion criteria following a first review of their medical records, and 30 had incomplete or missing data. Thus, 778 medical records with 3,034 specific ophthalmologic assessments related to AM were reviewed in detail and included in the study. We did not find statistical differences between included and excluded patients in relation to age and sex characteristics. These 778 patients started 869 different courses of treatment. The total follow-up of AM was 2,269 person-years, with a minimum of 5 days and a maximum of 17.5 years.

As shown in Figure 1, of the different courses of treatment, almost 40% were maintained, 53% were discontinued, while for 84 the follow-up was lost (including10 deaths, 4 patients moving to other health districts).

As seen in Table I, the patients were mostly women in their mid fifties. The main causes for receiving AM treatment were mostly RA or SLE, while the rest of the diagnoses included different forms of autoimmune and rheumatic disorders. In our setting two thirds of the patients received CQ, whereas the rest received HCQ, the latter being available in Spain only after the year 2002, and 10% of the patients used both AM at different times during the study period.

AM treatment discontinuation was permanent in 82% of the cases. The me-

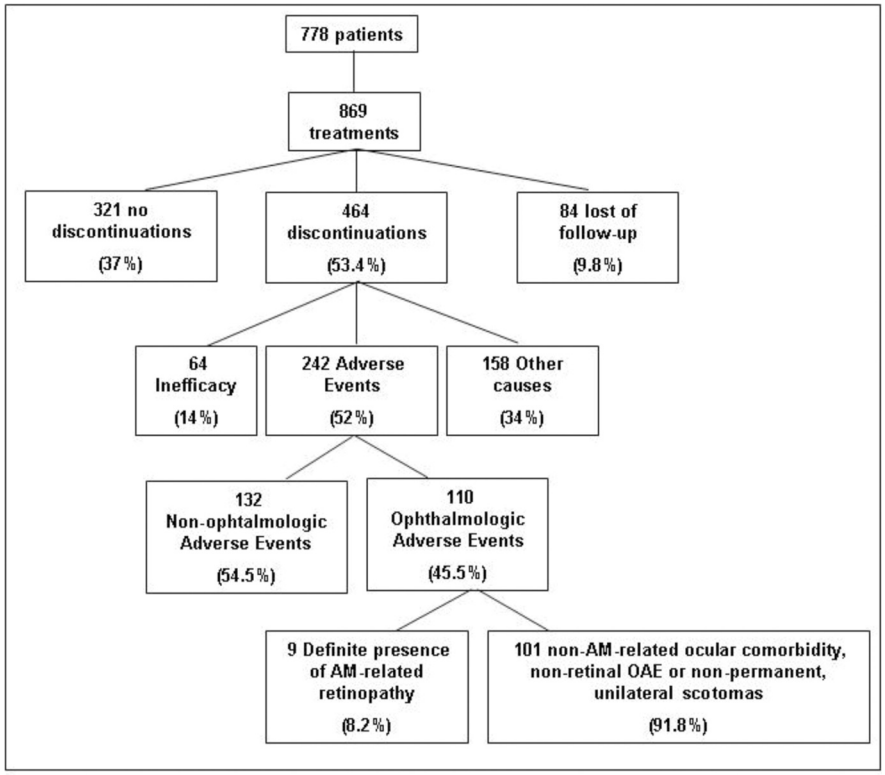

Fig. 1. Flow chart of the study.

Table I. Demographic and clinical characteristic of the study sample. Results are expressed as number (n) and percentage (%) unless otherwise is indicated.

	n. (%)
Female	631 (81.2)
Age at antimalarial start (years)*	53.59 ± 16.74
Diagnoses	
Rheumatoid arthritis	549 (70.6)
Systemic lupus erythematosus	119 (15.3)
Spondyloarthropathy	6 (0.7)
Psoriatic arthritis	12 (1.5)
Polymyalgia rheumatica	8 (1)
Sjögren syndrome	27 (3.4)
Juvenile idiopathic arthritis	3 (0.4)
Mixed connective tissue disease	20 (2.5)
Scleroderma / CREST	4 (0.5)
Other diseases‡	21 (2.7)
Antimalarial treatment	
Chloroquine	622 (71.7)
Hydroxychloroquine	246 (28.3)

*Age expressed as mean ± standard deviation.
‡ Others: inflammatory poliarthritis (47.5%), oligoarthritis (19%), hand osteoarthritis (9.5%), polyarteritis nodosa (4.8%), poliarthritis + Raynaud (4.8%), pleural effusion (4.8%), idiopathic purpura (4.8%) discoid lupus (4.8%).

dian AM survival time per treatment was 3.33 years (p25–p75 0.99–8.27 years), with an incidence rate of 204 per 1,000 patient-years (95% CI 186–224). As shown in the survival curve (Fig. 2), discontinuations were higher in the first 3 years. Factors associated with AM discontinuation in the multivariate analysis included ageing (HR=1.02; 95% CI 1.01–1.03), being a woman (HR=1.43; 95% CI 1.09–1.87), using both AM (HR=1.65; 95% CI 1.01–2.70); and SLE diagnosis when compared to RA (HR=0.58; 95% CI 0.44–0.77). The type of AM used did not have any statistical influence (HCQ *vs*. CQ HR=0.79; 95% CI 0.6–1.05).

The occurrence of adverse events (AE) was the main reason of discontinuation of the drugs with 242 AM treatments (52% of discontinuations) stopped for this cause, an incidence rate of 106.6 per 1,000 patient-years (95% CI 94–120.94), and a median survival of 8.38 years. Factors associated with AM discontinuation in the multivariate analysis included ageing (HR=1.02; 95% CI 1.01–1.03); using both AM (HR=2.93; 95% CI 1.54–5.59); and diagnosis of SLE and scleroderma when compared to RA (HR=0.38; 95% CI 0.23–0.65 and HR=2.8; 95% CI 1.08–7.45 respectively). The type of AM used did not have any statistical influence (HR of HCQ *vs*. CQ =0.72; 95% CI 0.48–1.06).

When the causes for AM discontinuation were analysed (Fig. 2), we found that non ophthalmologic adverse events (NOAE) represented more than half, (n=132 [54.5%]) of AM-related adverse events, with an incidence rate of 58.2 per 1,000 patient-years (95% CI 49.03–68.9), with most cases (68%) occurring in the first year (incidence rate in the first year: 137 per 1,000 patient-years [95% CI 111.9–169.1]) (Fig. 3). Gastrointestinal (43.5%), neuro-psychiatric (22%) and skin-related (18.3%) symptoms accounted for most causes of NOAE discontinuation. Most of them were mild except for two cases of epilepsy, one case of syncope with prolonged QT interval, and two tachycardia cases. Risk factors associated to increased NOAE discontinuation in the multivariate analysis included ageing (HR=1.02; 95% CI 1.01–1.03), diagnosis of SLE compared to RA (HR=0.25; 95% CI 0.10–0.60), and using both AM (HR=6.24; 95% CI 2.85–13.63). On the other hand, the type of AM used did not have any influence (p=0.82).

Another important cause of AM discontinuation was the occurrence of ophthalmologic adverse events (OAE). Indeed, treatment was discontinued in 110 cases for this reason (45.5% of AE-related AM-related adverse events). The median survival was 15.7 years, and the incidence rate of discontinuation was 48.5 per 1,000 patient-years (95% CI 40.12–58.14), and maintained through the survival curve. Most OAE discontinuations affected CQ treatments (88.2%), with an incidence rate of 53.4 per 1,000 patient-years (95% CI 43.17–65.1). HCQ accounted for 11.8% of discontinuations with an incidence rate of 29.7 per 1,000 patient-years (95% CI 16.6–49.4). The following factors were associated to discontinuation due to OAE in the multivariate model: ageing (HR=1.04; 95% CI 1.02–1.05) and type of AM used (HR of HCQ *vs*. CQ=0.34; 95% CI 0.15–0.76). Other associated factors included several diagnoses compared to RA: psoriatic arthritis (HR=4.16; 95% CI 1.26–13.71), MCTD (HR=2.67; 95% CI 1.32–5.42) and scleroderma (HR=2.66; 95% CI

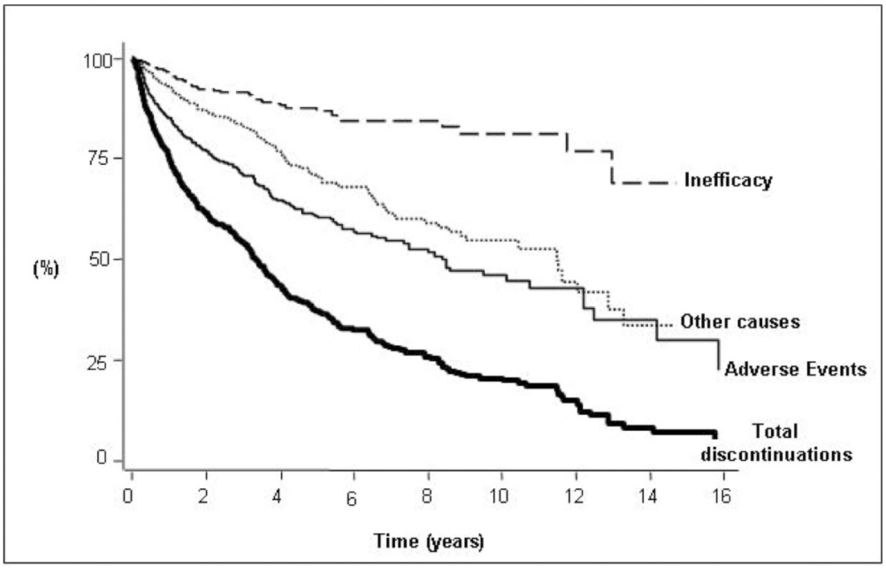

Fig. 2. Survival curves representing the percentage of AM treatments over time. The figure shows a global curve with all discontinuations, and also shows the different causes of discontinuations: inefficacy, adverse events, and other causes.

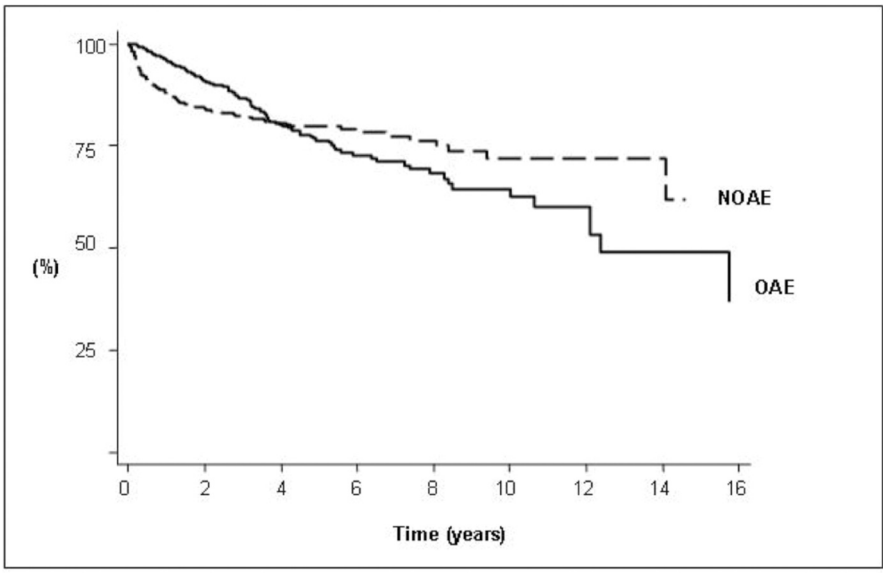

Fig. 3. Survival curves representing antimalarial discontinuation due to adverse events. Continuous line represents ophthalmologic adverse events (OAE) and dashed line represents non-ophthalmologic adverse events (NOAE). Percentages are referred to the total of adverse events.

1.17–6.05). The utilisation of both AM did not increase the risk (p=0.2).

When we analysed all ocular examinations of the 110 AM treatments allegedly discontinued due to OAE, we found that 9 (8%) were classified as AM-related definitive retinal toxicity, with an incidence rate of 3.97 per 1,000 patient-years (IC 95%: 2.06–7.62), which tends to increase over time (between 0 and 2 years: 1.8 [IC 95%: 0.4–7. 2], between 2 and 5 years: 4.5 [IC 95%: 1.4–14.0] and between 5 and 10 years: 10.1 [IC 95%: 3.2–31.4] per 1,000 patient-years). Table II shows the main characteristics of these patients. Out of 9 cases, 8 presented early asymptomatic retinopathy with permanent bilateral scotomas. The other patient developed an advanced bull's eye retinopathy and severe, irreversible loss of vision at 6.5 years of CQ treatment (incidence rate of 0.44 per 1,000 patient-years (IC 95%: 0.06–3.12). The time of presentation of retinopathy was variable, ranging from 1.9 years up to 12.11 years (mean 5.25±3.20). Nonetheless, half of the cases (55.5%) occurred in the first 5 years, including the only case on HCQ. These were women, with a mean age of 60 years, RA was diagnosed in 6 patients, and none of them had renal impairment at the beginning of the AM therapy. They received the antimalarial drug at conventional doses at the beginning of the treatment (250 mg/day for CQ and 200–400 mg/day for HCQ), and none of these patients had taken both drugs during the study period. Ageing (HR=1.07; 95% CI 1.04–1.12) and diagnosis of MCTD compared to RA (HR=4.24; 95% CI 1.75–10.31) were statistically associated with the development of AM-related definitive retinal toxicity in the multivariate analysis, whereas type of AM used did not have any influence (p=0.81).

We found that in 64 (14%) cases the cause of discontinuation was the lack of efficacy, with an incidence rate of 28 per 1,000 patient-years (95% CI 22–36) that was maintained through the survival curve. In the regression model, the only variable associated to discontinuation due to lack of efficacy was the diagnosis (polymyalgia rheumatica compared to RA HR=10.16; 95% CI 2.78–37.11). Although SLE had a lower probability for discontinuation, it was not significant (HR=0.54; 95% CI 0.26–1.08; p=0.08). Other causes of discontinuation accounted for roughly a third, 158 (34%), of treatment discontinuations. These included: 55 cases for fear or refusal to take the medication; 31 for non-AM-related ocular comorbidity; 15 patients with remission; 11 pregnancy-related cases; 12 miscellaneous (unspecified medical decision); and 34 unreported causes. It is important to note that non-AM-related ophthalmologic problems included mostly cataracts or macular disease that probably interfered with screening for AM toxicity. Ageing was the only factor statistically associated with discontinuation by these non-AM-related ophthalmologic problems (HR: 1.03; 95% CI 1.01–1.05).

The other 101 AM treatments allegedly discontinued due to ocular toxicity were classified as: a) 32 cases of non-retinal OAE (all of them corneal deposits); b) 10 non-permanent, unilateral scotomas; and c) 62 cases of non-AM-related oc-

Table II. Main features of the patients with definite ophthalmological toxicity related to antimalarials.

Patient	Age*	Disease	AM	Weight (kg)	Treatment duration	Main ophthalmologic findings
1	72.7	RA	CQ	90	1 yr 11 m	Macular depigmentation Central scotoma†
2	63.4	Sjögren	CQ	71	4 yr 1 m	Macular depigmentation Central scotoma†
3	52.7	MCTD	CQ	83	12 yr 1 m	Macular depigmentation
4	60.0	RA	CQ	64	5 yr 4 m	Macular depigmentation Central scotoma†
5	54.2	RA	HCQ	70	3 yr 6 m	Macular depigmentation Central scotoma†
6	53	RA	CQ	68	3 yr 2 m	Central scotoma†
7	63.6	RA	CQ	66	7 yr 11 m	Macular depigmentation
8	72	RA	CQ	70	2 yr 9 m	Macular depigmentation Central scotoma†
9	47.5	SLE	CQ	74.5	6yr 6 m	Bull's eye maculopathy

*Age at antimalarial start, expressed in years. All are females.
RA: rheumatoid arthritis; MCTD: mixed connective tissue disease; SLE: systemic lupus erythematosus; CQ: chloroquine; HCQ: hydroxychloroquine; yr: year; m: month.
†Visual field test (Humphrey 10–2 fields).

ular comorbidity. All the patients classified in the two former situations were asymptomatic and without significant loss of their visual acuity.

Discussion

We have analysed the use and causes of discontinuation of CQ and HCQ in a large cohort of rheumatologic patients. We found a number of discontinuations due to treatment inefficacy, the occurrence of adverse effects and other causes. However, retinal toxicity was observed in 9 patients, of which one case resulted in irreversible loss of vision, suggesting that AM treatments could have a good balance between benefit and risk.

Our cohort of 778 patients is representative of the use of AM, the majority of which were women who started the treatment in the fifth decade of their life after being diagnosed with RA (70%), SLE (15%) or other autoimmune disorders, in agreement with other studies (1, 2). These characteristics, in addition to the relatively large number of patients included, and the longitudinal, standardised follow-up covering more than seventeen years for some patients, suggest that our findings might be extended to most patients attended in a variety of clinical settings. However, we would like to emphasise that our cohort included a large proportion of CQ patients, mainly because HCQ was available in Spain only after year 2002. In this sense, our long-term data regarding CQ have a stronger support than those regarding HCQ (1,816 person*years for CQ and 454.5 person*years for HCQ).

We found that more than fifty percent of the AM treatments were discontinued, with a median AM use of 3.33 years. Two thirds of the discontinuation cases occurred in the first five years and the remaining third was distributed in the next six to ten years (Fig. 2). This pattern is attributable to the fact that most of the NOAE were mild, which occurs in the initial phase of treatment, in agreement with other studies (2, 4). As expected (9, 14, 26), we found age- and gender-related discontinuation causes, since treatment discontinuation was higher in elder women. Interestingly, it seems that SLE patients tolerate better AM than RA patients probably related to a good response to the drug, with a significantly lower discontinuation rate specifically due to NOAE. Metabolic reasons, genetic factors and/or interactions with other drugs could explain these results. It is also important to note that AM showed a lower rate of discontinuation than that reported for other disease-modifying antirheumatic drugs (DMARDs) (9, 11) that might have more severe adverse events and in fact need closer monitoring, suggesting a good safety profile of AM.

When withdrawal causes were analysed separately, lack of efficacy accounted for 14% of the discontinuations, with no differences between CQ (incidence rate of per 1,000 patient-years [IR]: 28.0 [IC 95%: 21–37]) and HCQ (IR: 28.7 [IC 95%:16-6–49.5]). Previous studies showed higher inefficacy-related discontinuation rates mainly for HCQ (2, 27). However, this observation might be biased due to the progressive introduction of combined therapy in RA, with an increasing tendency to add a second or third DMARD after initial treatment failure. Another possible explanation is the intrinsic limitation of our retrospective study that stems from the fact that causes of discontinuation might not be clearly stated in the medical records and thus classified as other reasons of discontinuation.

Adverse events were the main cause of AM discontinuation, occurring in approximately 50% of the cases, with a slightly greater proportion of patients ending treatment for NOAE compared to OAE. As stated above, NOAE and OAE behaved differently overtime. While the former showed an accelerated phase during the first year, the latter maintained a more stable rate of discontinuation over time (median discontinuation almost 16 years), supporting different mechanisms for different adverse events.

NOAE accounted for 54.5% of AE-related discontinuations, with gastrointestinal symptoms as the main cause, followed by neuro-psychiatric problems, skin reactions, and a small number of other causes. This percentage seems to be higher than that reported in other studies (2, 21, 28), but the differences might be attributable to the different methodologies employed, given that the characteristics of NOAE were similar.

Most of them were slight and transient, recovering soon after discontinuation of the drug, and a tendency to a slower recovery of ear, nose and throat, and muscular problems (data not shown). Half the patients switching from CQ to HCQ were able to maintain long-term

treatment with the latter. Although it has been suggested that there were differences in toxicity between AM (2, 27), we did not find statistical differences between CQ and HCQ in relation to NOAE-related discontinuations (incidence rate per 1,000 patient-years [IR] of: 54 [IC 95%: 44.7–66-3] for CQ and 72 [IC 95%: 51.8–102.6] for HCQ). In our patients, exposure to one antimalarial followed by a second exposure to other antimalarial was associated with a higher probability to develop NOAE, probably reflecting common mechanisms of toxicity. As expected, age was associated with NOAE discontinuation (26, 29).

Development of OAE was another important cause of discontinuation in our study. A definitive retinal toxicity was confirmed in 9 patients when discontinuations were analysed by an expert ophthalmology team, representing 1.03% of the treatments, with no differences between AM utilisation (2). This percentage is slightly higher than that observed in some studies (2, 4, 26, 30-33), but similar to that reported in others (21, 28, 33-36). Discrepancies might be influenced by the greater use of CQ in our study, the intrinsic differences of each cohort, and/or different end points and analyses employed in each individual study. All the patients with definitive retinal toxicity received the AM at conventional doses (250 mg/day for CQ and 400 mg/day for HCQ) (26).

Eight of the definitive retinal toxicity cases were detected in the initial stages of retinal toxicity without clinical repercussion; unfortunately, one of the patients suffered a significant decrease in visual acuity. This patient had SLE and had received CQ for 78 months at a dose of 3.35 mg/kg/day. As showed by other authors (33, 36), definitive retinal toxicity increases over time. However, one of the cases reported here appeared in the first two years following the initiation of the treatment, and half of the remaining cases occurred in the first five years.

The rest of discontinuations related to OAE, 101, were due to ophthalmologic problems that are not usually considered a cause for compulsory AM discontinuation, with a higher risk for CQ than for HCQ, in accordance with Aviña-Zubieta (2). These findings included: asymptomatic AM-corneal-deposits, unilateral non-persistent scotomas, or age-related macular disease. This result raises the question on the adequacy of drug discontinuation in those patients of our cohort that presented with ocular findings that are generally considered as non-related to serious retinal toxicity.

Other causes, accounting for a third of all discontinuations, included other common situations that occur with non selected patients in real-life conditions. These causes included fear or refusal to take the medication, pregnancy, and age-related eye comorbidity, mostly cataracts and macular disease. The latter probably reflects the intrinsic difficulties of managing the safety of patients when an eventual loss of vision is present in the equation.

On the one hand, our results suggest that AM have a good safety profile. On the other hand, the potential for an unusual but serious ophthalmologic toxicity creates two different challenges. The first is the need to perform specific, periodical, ophthalmologic examinations in order to detect early signs of retinal toxicity (37-38). Our findings reveal that performing at least yearly examinations helps to identify early retinal damage in order to avoid the possibility of visual loss. Moreover, in accordance with other authors, we detected early cases of retinal toxicity (26, 33, 36, 39) in patients using the recommended AM doses (26). These results might warn against recent recommendations tending to either loosen the follow-up system or to start eye examinations after five years of AM treatment (17, 19). The second challenge is to avoid AM discontinuation in a number of patients with good response that develop either non-significant AM-related toxicity in ophthalmologic examinations, aged-related visual problems or fear to take the medication. These causes of AM discontinuation accounted for more than a third of the total causes of discontinuations in our setting, thus emphasising the need for a team-based approach that includes ophthalmologists, clinicians and the patients themselves, in order to decrease the number of unnecessary AM discontinuations. This is particularly important, given the higher toxicity potential of alternative treatments.

In conclusion, this work provides a better knowledge of the causes and risk factors associated to antimalarial drug discontinuation. Furthermore, it stresses the need for a more individualised monitoring system to predict and detect early AM-related retinal toxicities, in order to increase the safety and quality of care of AM patients.

References

1. RYNES RI: Antimalarial drugs in the treatment of rheumatological diseases. *Br J Rheumatol* 1997; 36: 799-805.
2. AVINA-ZUBIETA JA, GALINDO-RODRIGUEZ G, NEWMAN S, SUAREZ-ALMAZOR ME, RUSSELL AS: Long-term effectiveness of antimalarial drugs in rheumatic diseases. *Ann Rheum Dis* 1998; 57: 582-7.
3. WALLACE DJ: Antimalarial agents and lupus. *Rheum Dis Clin North Am* 1994; 20: 243- 63.
4. MORAND EF, MCCLOUD PI, LITTLEJOHN GO: Continuation of long term treatment with hydroxychloroquine in systemic lupus erythematosus and rheumatoid arthritis. *Ann Rheum Dis* 1992; 51: 1318-21.
5. WALLACE DJ, LINKER-ISRAELI M, HYUN S, KLINENBERG JR, STECHER V: The effect of hydroxychloroquine therapy on serum levels of immunoregulatory molecules in patients with systemic lupus erythematosus. *J Rheumatol* 1994; 21: 375.
6. WOZNIACKA A, LESIAK A, NARBUTT J, MCCAULIFFE DP, SYSA-JEDRZEJOWSKA A: Chloroquine treatment influences proinflammatory cytokine levels in systemic lupus erythematosus patients. *Lupus* 2006; 15: 268-75.
7. ALETAHA D, SMOLEN JS: The rheumatoid arthritis patient in the clinic: comparing more than 1,300 consecutive DMARD courses. *Rheumatology* (Oxford) 2002; 41: 1367-74.
8. SCHMAJUK G, YAZDANY J, TRUPIN L, E Y: Hydroxichloroquine treatment in a community -based cohort of patients with systemic lupus erythematosus. *Arthritis Care Res* 2010; 62: 386-92.
9. ALETAHA D, T KAPRAL T, J S SMOLEN SJ: Toxicity profiles of traditional disease modifying antirheumatic drugs for rheumatoid arthritis. *Ann Rheum Dis* 2003; 62: 482-6.
10. PARKE A, WEST B: Hydroxychloroquine in pregnant patients with systemic lupus erythematosus. *J Rheumatol* 1996; 23: 1715-8.
11. RUNGE LA: Risk/benefit analysis of hydroxychloroquine sulfate treatment in rheumatoid arthritis. *Am J Med* 1983; 75: 52-6.
12. WETTERHOLM DH, WINTER FC: Histopathology of chloroquine retinal toxicity. *Arch Ophthalmol* 1964; 71: 82-7.
13. BERNSTEIN HN, J G: The pathology of chloroquine retinopathy. *Arch Ophthalmol* 1964; 71: 238-45.
14. EASTERBROOK M: Detection and prevention of maculopathy associated with antimalarial

agents. *Int Ophthalmol Clin Spring* 1999; 39: 49-57.
15. FINBLOOM DS: Comparison of hydroxychloroquine and chloroquine use and development of retinal toxicity. *J Rheumatol* 1985; 12: 692-4.
16. RAINES MF, BHARGAVA SK, ROSEN ES: The blood-retinal barrier in chloroquine retinopathy. *Invest Ophthalmol Vis Sci* 1989; 30: 1726-31.
17. MARMOR MF, CARR RE, EASTERBROOK M, FARJO AA, MIELER WF; AMERICAN ACADEMY OF OPHTHALMOLOGY: Recommendations on screening for chloroquine and hydroxychloroquine retinopathy: a report by the American Academy of Ophthalmology. *Ophthalmology* 2002; 109: 1377-82.
18. RYNES RI, BERNSTEIN HN: Ophthalmologic safety profile of antimalarial drugs. *Lupus* 1993; 2 (Suppl. 1): S17-19.
19. THE ROYAL COLLEGE OF OPHTHALMOLOGISTS: Hydroxychloroquine and Ocular Toxicity Recommendations on Screening. *London BSR* 2009; October: 1-9.
20. BERNSTEIN HN: Ophthalmologic considerations and testing in patients receiving long-term antimalarial therapy. *Am J Med* 1983; 18; 75: 25-34.
21. WANG C, FORTIN PR, LI Y, PANARITIS T, GANS M, ESDAILE JM: Discontinuation of antimalarial drugs in systemic lupus erythematosus. *J Rheumatol* 1999; 26: 808-15.
22. WOLFE F, HAWLEY DJ, CATHEY MA: Termination of slow acting antirheumatic therapy in RA: a 14 year prospective evaluation of 1017 consecutive starts. *J Rheumatol* 1990; 17: 994-1002.
23. EASTERBROOK M: The ocular safety of hydroxychloroquine. *Semin Arthritis Rheum* 1993; 23 (Suppl. 1): 62-7.
24. BERNSTEIN HN: Ocular safety of hydroxychloroquine. *Ann Ophthalmol* 1991; 23: 292-6.
25. EASTERBROOK M: Ocular effects and safety of antimalarial agents. *Am J Med* 1988 Oct 14; 85: 23-9.
26. MACKENZIE AH: Dose refinements in long-term therapy of rheumatoid arthritis with antimalarials. *Am J Med* 1983; 75 (Suppl. 1A): 18-40.
27. FELSON DT, ANDERSON J, MEENAN RF: The comparative efficacy and toxicity of second-line drugs in rheumatoid arthritis. *Arthritis Rheum* 1990; 33: 1449-61.
28. ADAMS EM, YOCUM DE, BELL CL: Hydroxychloroquine in the treatment of rheumatoid arthritis. *Am J Med* 1983; 75: 321-6.
29. AYLWARD JM: Hydroxychloroquine and chloroquine: assessing the risk of retinal toxicity. *J Am Optom Assoc* 1993; 64: 787-97.
30. LEVY GD, MUNZ SJ, PASCHAL J, COHEN HB, PINCE KJ, PETERSON T: Incidence of hydroxychloroquine retinopathy in 1,207 patients in a large multicenter outpatient practice. *Arthritis Rheum* 1997; 40: 1482-6.
31. MORSMAN CD, LIVESEY SJ, RICHARDS IM, JESSOP JD, MILLS PV: Screening for hydroxychloroquine retinal toxicity: is it necessary? *Eye* (Lond) 1990; 4: 572-6.
32. SPALTON DJ: Retinopathy and AM drugs – the British experience. *Lupus* 1996; 5 (Suppl. 1): S705-25.
33. YAM JC, KWOK AK: Ocular toxicity of hydroxychloroquine. *Hong Kong Med J* 2006; 12: 294-304.
34. MAVRIKAKIS I, SFIKAKIS PP, MAVRIKAKIS E *et al*.: The incidence of irreversible retinal toxicity in patients treated with hydroxychloroquine: a reappraisal. *Ophthalmology* 2003; 110: 1321-6.
35. MARKS JS: Cloroquine retinopathy: Is there a safe daily dose? *Ann Rheum Dis* 1982; 41: 52-8.
36. WOLFE F, MARMOR MF: Rates and predictors of hydroxychloroquine retinal toxicity in patients with rheumatoid arthritis and systemic lupus erythematosus. *Arthritis Care Res* 2010; 62: 775-84.
37. PEPONIS V, KYTTARIS V, CHALKIADAKIS S, BONOVAS S, SITARAS NM: Ocular side effects of anti-rheumatic medications: what rheumatologist should know. *Lupus* 2010; 19: 675-82.
38. KOBAK S, DEVECI H: Retinopathy due to antimalarial drugs in patients with connective tissue diseases: are they so innocent? A single center retrospective study. *Int J Rheum Dis* 2010; 13: e11-5.
39. PUAVILAI S, KUNAVISARUT S, VATANASUK M *et al*.: Ocular toxicity of chloroquine among Thai patients. *Int J Dermatol* 1999; 38: 934-7.