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Antimalarial drug toxicities in patients with cutaneous lupus and dermatomyositis: a retrospective cohort study

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Abstract

Background—Although existing evidence demonstrates the efficacy of antimalarials for rheumatic skin disease, the safety of these medications, and particularly quinacrine, remain debated.

Objective—We investigate the toxicity risk associated with antimalarials in patients with cutaneous lupus erythematosus (CLE) and dermatomyositis (DM).

Methods—532 patients (Mean age=52.29 years, Female=85.15%, Male=14.85%) were selected from two databases of CLE (69.92%) and DM (30.08%). Details regarding treatment and toxicities were extracted and five treatment courses were defined [i.e., hydroxychloroquine (HCQ), chloroquine (CQ), quinacrine (Q), hydroxychloroquine-quinacrine (HCQ-Q), and chloroquine-quinacrine (CQ-Q)]. The hazard ratio for each major toxicity was estimated using the Cox proportional hazard model to compare the different treatments to HCQ.

Results—The most common toxicities included cutaneous eruption, gastrointestinal (GI) upset, mucocutaneous dyspigmentation, neurologic, and retinopathy. Compared to HCQ, the hazards of cutaneous eruption, GI upset, and neurologic toxicities were lower with HCQ-Q; however, this may represent selection bias. Although there was increased retinopathy risk with CQ and CQ-Q relative to HCQ, retinopathy was not seen with Q.

Limitations—Retrospective analysis

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Conclusions—With the exception of retinopathy, which was not seen with quinacrine, the risks of other toxicities associated with quinacrine monotherapy or combinational treatment were not significantly different than with hydroxychloroquine.

Keywords

Hydroxychloroquine; Chloroquine; Quinacrine; Cutaneous Lupus Erythematosus; Dermatomyositis; Drug Reactions

Introduction

Antimalarials are historically the cornerstone of treatment for systemic and cutaneous lupus erythematosus (CLE). Hydroxychloroquine, chloroquine, and quinacrine are key medications for patients with LE and are frequently used chronically. These drugs have demonstrated a response rate greater than 50% for CLE, and their use has been expanded to various other inflammatory conditions.¹ The step-wise algorithm involves an initial trial of hydroxychloroquine followed by the addition of quinacrine if hydroxychloroquine monotherapy fails. Chloroquine is ultimately added, often also in combination with quinacrine, if hydroxychloroquine and quinacrine combination therapy fails.²

Recently there has been renewed interest in quinacrine. This drug has synergistic efficacy when given as part of an antimalarial combination and has demonstrated therapeutic promise for recalcitrant disease.^{3,4} Emerging evidence suggests that this effect may be because quinacrine has a distinct mechanism compared to its counterparts involving the downregulation of TLR-3, -4 and -8 responses.^{5,6} Quinacrine has been compounded since the early 1990's when production was discontinued by Sanofi-Winthrop.⁷ In March 2016, the Pharmacy Compounding Advisory Committee (PCAC) examined quinacrine as part of its regular monitoring of compounded drugs which is mandated by the Drug Quality and Security Act (2013).

After weighing disparate recommendations from infectious disease, rheumatology, and reproductive health specialists, the Office of New Drugs (OND) voted to discontinue compounding of this medication for all indications. They further recommended that for patients who are intolerant or unresponsive to approved alternate therapies, quinacrine could be prescribed through an Investigational New Drug application (IND). This would require Institutional Review Board (IRB) approval and patient consent.⁸ If approved, these regulatory requirements may severely restrict availability of quinacrine for all uses. The FDA's concerns were primarily based on World War II reports of quinacrine-associated aplastic anemia and hepatitis, which occurred at dosages exceeding the standard 100-mg/day dose typically prescribed for rheumatic skin disease.⁸

Based on these recent PCAC proceedings, there remains a lack of consensus on the risk of toxicities associated with quinacrine and other drugs in its class. Most commonly, quinacrine causes transient gastrointestinal (GI) upset, yellow skin discoloration, and headache.⁹ Retinal toxicity, the most feared complication associated with hydroxychloroquine (HCQ) or chloroquine (CQ) therapy, is not known to occur with quinacrine (Q). The retinopathy risk is greater with CQ which is why this drug is typically reserved for patients refractory to HCQ

and Q combination treatment.¹⁰ Other serious toxicities associated with HCQ and CQ include cardiomyopathy,¹¹ myopathy,¹² and ototoxicity¹³. Certain reversible but more common adverse effects include GI discomfort and mucocutaneous blue-black dyspigmentation.¹⁴

The body of clinical experience with quinacrine reflects its efficacy and safety, particularly for patients with recalcitrant disease and those at risk for antimalarial induced retinopathy. Given that Q is used frequently, it is critical to investigate the risk of toxicities associated with this drug relative to others in its class.¹⁵ Additionally, because Q is typically given in combination with either HCQ or CQ, it is also necessary to determine whether combinational therapy impacts the risk of antimalarial induced toxicities. In this study, we investigate the incidence over time and the risks of toxicities associated with HCQ, CQ, and Q monotherapies, as well as HCQ + Q and CQ + Q combinations in patients with rheumatic skin diseases.

Methods

Subject Selection

In this retrospective cohort study, patients were selected from two longitudinal databases of cutaneous lupus erythematosus (CLE) and dermatomyositis (DM) that have been ongoing since January 2007 and January 2008, respectively. Both databases were initiated by the principle investigator's research team and consist of patients seen at the outpatient autoimmune skin disease clinic of the Hospital of the University of Pennsylvania (HUP). Those included in this study have been enrolled in the databases since their creation and were accessed for this study until August 2016. Those without a history of antimalarial treatment were excluded. Additionally, patients for whom there are no records following antimalarial initiation were excluded because the ability to tolerate the medication(s) cannot be determined for this subset (see Figure 1). All patients in these databases are 18 years of age and have a clinicohistopathologic diagnosis of either CLE or DM (Table I).

Data Collection

Information in the CLE and DM databases is collected prospectively when enrolled patients attend regularly scheduled clinic visits at HUP. In the medication history of the database records, a toxicity is attributed to a drug if it is clinically characteristic of a side effect known to be associated with that medication. This determination may be based on a combination of the patient's symptoms, physical exam findings, a temporal association between treatment initiation or discontinuation and appearance or resolution of toxicity, respectively, as well as results of diagnostic testing reports. In the case of antimalarial induced retinopathy, affected patients had either subjective complaints of visual deficits or ophthalmology reports including results of Humphrey Visual Field test, optical coherence tomography (OCT), or multifocal electroretinography (mfERG) evidencing the drug toxicity.

For this study, database records were reviewed to extract details regarding antimalarial drug use and history of toxicities related to treatment. The types of antimalarial medications, the initiation and discontinuation dates of therapy, the types of antimalarial-induced toxicities

that occurred, and the initial dates of these episodes were collected. For a given date, if only the month of a year or simply the year was available, then the first day of that particular month or of the year was recorded, respectively. Similarly, if only a particular season was available for a certain date, for example, summer 2010, then the first day of the season was recorded.

Statistical Analysis

To analyze the relationship between toxicities and antimalarial treatment over time, a treatment course was defined as the duration of a monotherapy or combination of antimalarial drugs. The start of the course was designated the initiation date of therapy, and the end was the discontinuation of therapy for any reason. A course was considered continuous if it included no more than one month of a missed dose given the lengthy elimination half-lives of antimalarials.¹⁰

The five different treatment courses included hydroxychloroquine monotherapy (HCQ), chloroquine monotherapy (CQ), quinacrine monotherapy (Q), hydroxychloroquine-quinacrine combination (HCQ-Q), and chloroquine-quinacrine combination (CQ-Q). No patients had a HCQ-CQ combination course because these two drugs are never combined due to their additive risk of retinal toxicity. Patients often had a history of multiple types of treatment courses because therapy is typically modulated over time (Table II). 41.7% (n=222) of patients began with HCQ and later switched to either HCQ-Q or Q. Additionally, 16.9% (n=90) of patients initially took HCQ or Q monotherapy or HCQ-Q combination and then switched to either CQ or CQ-Q. Patients recorded as having started with antimalarial combinations different from HCQ monotherapy usually had other regimens prior to their enrollment in the CLE and DM databases.

The absolute incidences of toxicities were calculated, and the incidences of the five most common toxicities per one person-year of each antimalarial treatment course were determined. A given toxicity was attributed to a treatment course as long as it occurred during a treatment course or within two weeks of discontinuing the corresponding antimalarial regimen. For the five most common toxicities, the time to event was defined as the time between treatment initiation and toxicity occurrence. A subject was censored if toxicity did not occur by the end of the follow-up period. The time to each type of toxicity on different antimalarial combinations was summarized using Kaplan-Meier survival curves. Then, for each toxicity type, the hazard ratios comparing the different antimalarials to HCQ were estimated using the Cox proportional hazard model, adjusted for sex, race (white vs. nonwhite), smoking status (never smoker vs. smokers), and age at baseline visit. To compare the hazard rates of each toxicity between HCQ and each other treatment course, Bonferroni-adjusted significance levels were used according to the number of comparisons conducted within each Cox model. All statistical analyses were performed using SAS ® 9.4.

Results

The most common toxicities associated with antimalarials included cutaneous eruption (n=61), gastrointestinal (GI) upset (n=38), mucocutaneous dyspigmentation (n=26), neurologic side effects [i.e., including dizziness and headache (n=10), ototoxicity (n=5),

sleep disturbances (n=5), mental fog (n=5), peripheral neuropathy (n=4), tremors (n=2), and psychosis (n=1)] and retinopathy (n=17) (Table III). The two patients with only subjective complaints of decreased visual acuity were excluded from additional statistical analysis, and only those with objective evidence (n=15) of ocular toxicity based on standard ophthalmologic exam findings (e.g., bull's eye pattern of damage on OCT) were further analyzed. The incidence of these toxicities per one person-year of treatment with five different combinations of antimalarials were 0–0.073 for cutaneous eruption, 0.013–0.057 for GI upset, 0–0.476 for mucocutaneous dyspigmentation, 0–0.045 for neurologic toxicities, and 0–0.004 for retinopathy (Appendix).

Compared to HCQ monotherapy, the risk of cutaneous eruption was significantly lower with HCQ-Q combination therapy (HR 0.231, 95% simultaneous CI (0.07–0.82), $p=0.0056$). The hazard of cutaneous eruption with other antimalarial combinations was not significantly different from that of HCQ. Additionally, the hazard of GI upset on HCQ-Q combination was much smaller than that for HCQ monotherapy (HR=0.229), though the difference was just close to being statistically significant ($p=0.0157$). Compared to HCQ, the hazards of retinopathy were significantly greater with both CQ (HR 30.349, 95% CI (1.50–613.30), $p=0.006$ and CQ-Q (HR 26.664, 95% CI (21.64–432.37), $p=0.0049$) (Table IV).

A post-hoc analysis was performed to analyze whether patients that developed toxicity on HCQ or CQ monotherapy were less likely to later receive HCQ-Q or CQ-Q combination therapy, respectively. A lower percentage of those with certain toxicities on HCQ later received HCQ-Q combination as compared to those without toxicity to HCQ (cutaneous eruption: 11.1% vs. no cutaneous eruption: 37.7%, GI upset: 22.2% vs. no GI upset: 55.7%, neurologic toxicities: 27.3% vs. no neurologic toxicities: 36.2%, retinopathy: 0% vs. no retinopathy: 36.2%). HCQ-Q was later given to a greater percentage of those with dyspigmentation (50%) on HCQ versus those without dyspigmentation (35.5%). Of those with GI upset and ophthalmic toxicity to CQ, none later received CQ-Q. Cutaneous eruption, dyspigmentation, and neurologic toxicities did not occur with CQ.

Discussion

Over 90% of our patients had a history of HCQ, and nearly half (42.9%) had a history of HCQ-Q. Only ~20% of patients had a history of CQ either as monotherapy (11.1%) or in combination with quinacrine (10.2%). Over half of the patients had a history of Q, usually in combination with HCQ or CQ, but also as monotherapy (11.8%). This pattern is consistent with the step-wise algorithm for antimalarials in rheumatic skin disease and also illustrates the substantial proportion of patients reliant on a combinational regimen.

Consistent with prior literature, the most prevalent toxicities in our sample included cutaneous eruption, GI upset, mucocutaneous dyspigmentation, neurologic toxicities including primarily headache and dizziness, and retinopathy. The incidences of retinopathy per person-year of various antimalarial treatment combinations were relatively lower than those of the other toxicities. This may be due to the time dependent nature of retinal toxicity, the risk of which is under 1% after five years but rises to 20% after twenty years of antimalarial use.^{16,17} Importantly, although retinopathy may be rarer than other toxicities, it

is often irreversible and more serious. Conversely, cutaneous eruption had the highest incidence per person-year of treatment with HCQ. This may reflect the shorter time period that typically elapses between drug initiation and development of a hypersensitivity skin reaction. Relative to HCQ, the combination of HCQ-Q was associated with significantly lower risk of cutaneous eruption. Additionally, consistent with prior evidence on the greater association of retinopathy with CQ as compared to HCQ, we found an increased risk of retinopathy with CQ and CQ-Q relative to that of HCQ.

Our post-hoc analysis was to determine whether our findings represent a protective benefit of Q or the selection of individuals able to tolerate HCQ in the cohort of patients with a history of HCQ-Q. We indeed found that compared to patients with an unremarkable HCQ course, those who experienced cutaneous eruption, GI upset, neurologic toxicities, and retinopathy on HCQ were less likely to later receive HCQ-Q. Interestingly, this pattern did not apply to dyspigmentation. This may be because dyspigmentation resolves with continued use and does not cause bothersome physical symptoms beyond its cosmetic inconvenience. However, this is purely speculative.

Although a protective benefit of Q is unlikely based on our analysis, these findings suggest that combining Q with HCQ or CQ does not increase the risk of toxicity associated with these drugs. Notably, there were no cases of retinal toxicity with Q. Additionally, there were no cases of aplastic anemia or severe hepatitis due to Q. Although these two serious adverse effects are the basis of the FDA's concern with quinacrine, WWII records indicate that they occurred in only 1/500,000 soldiers. Additionally, these toxicities have not been reported at a 100-mg/day dose.^{9,18–22} Compared with HCQ, there was no significant difference in the risk of any common toxicity (i.e., cutaneous eruption, GI upset, dyspigmentation, and neurologic toxicities) associated with Q.

The main limitation of this study is its retrospective nature. We attributed toxicities to the treatment(s) patients were taking either at the time or two weeks prior to the event occurrence. Although this may be suitable for toxicities that occur relatively quickly following treatment initiation (i.e., cutaneous eruption), it is imperfect for retinal toxicity, which is time-dependent. Seven of the fifteen patients with retinopathy developed these deficits towards the end of their initial antimalarial course. The remaining developed retinopathy towards the end of a second or third treatment course. In these cases, retinal changes did not develop until 9 months–20 years (median=6 years, 95% CI= 2.85–9.35 years) following initiation of the treatment course to which the toxicity was attributed. Additionally, the most recent screening guidelines for antimalarial retinopathy recommend annual screening after five years for patients without major risk factors.¹⁷ Given that all patients on HCQ and CQ in our cohort received annual ophthalmic exams, it is unlikely that retinal changes started during prior treatment courses in this subgroup.

Two patients (0.38%) in our cohort presented with subjective complaints of visual blurring after starting antimalarials but did not have objective evidence of retinal damage. Future investigations may determine the incidence and risk of antimalarial-induced non-retinal complications, which may be currently under-recognized.²³ Additionally, we did not examine the impact of dosages on the development of toxicities as most patients were on

standard antimalarial dosages, which were infrequently altered (e.g., 200–400 mg/day of HCQ, 100 mg/day of Q, and 250 mg/day of CQ). Finally, the focus of this study was on established antimalarial toxicities as opposed to the detection of new side effects. Future studies are needed to investigate the impact of cumulative dosages on toxicities and to potentially discover new antimalarial toxicities.

Our study provides evidence that the safety profile of Q is not statistically significantly different from that of HCQ and that Q has an advantage over HCQ and CQ for patients at risk of retinopathy. Adding Q to HCQ or CQ does not increase the risk of toxicities based on our results, and limiting access to Q may leave patients without alternatives to this safe drug. Before making a final decision about the future availability of Q, we must continue examining the true safety risks associated with this important class of medications.

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Abbreviations List

CLE	Cutaneous Lupus Erythematosus
DM	Dermatomyositis
SLE	Systemic Lupus Erythematosus
TLR-4 & TLR-8	Toll Like Receptor 4 & Toll Like Receptor 8
FDA	Food and Drug Administration
PCAC	Pharmacy Compounding Advisory Committee
IND	Investigational New Drug
IRB	Institutional Review Board
HUP	Hospital of the University of Pennsylvania
OCT	Optical Coherence Tomography
mfERG	Multifocal Electroretinography
HCQ	Hydroxychloroquine Monotherapy
CQ	Chloroquine Monotherapy
Q	Quinacrine Monotherapy
HCQ-Q	Hydroxychloroquine-Quinacrine Combination Therapy

CQ-Q	Chloroquine-Quinacrine Combination Therapy
GI	Gastrointestinal
HR	Hazard Ratio

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Appendix. Incidence of most common toxicities per one person-year of each antimalarial treatment course combination

	Cutaneous Eruption	GI Upset	Dyspigmentation	Neurologic Toxicities	Retinal Toxicity
HCQ	0.0731	0.0569	0.0163	0.0447	0.0041
CQ	0.0339	0.0169	0	0.0159	0.0339
Q	0	0.0476	0.0476	0	0
HCQ-Q	0.0175	0.0132	0.0219	0.0088	0.0044
CQ-Q	0.0556	0.0370	0.0185	0.0370	0.0056

HCQ = hydroxychloroquine; CQ = chloroquine; Q = quinacrine; HCQ-Q = hydroxychloroquine + quinacrine; CQ-Q = chloroquine + quinacrine

Figure 1.
Patient Selection

Table I

Baseline Characteristics of Study Subjects

Characteristics	Frequency (%) (n=532)
Sex	
Male (%)	79 (14.85%)
Female (%)	453 (85.15%)
Race	
Asian	16 (3.01%)
Black	124 (26.32%)
White	371 (69.74%)
Other	18 (29.70%)
Unknown	3 (0.56%)
Ethnicity	
Hispanic	15 (2.82%)
Non-Hispanic	513 (96.43%)
Unknown	4 (0.75%)
Age at baseline visit	52.29 (+/-14.67 years)
Follow-up periods	6.98 years (+/-6.83 years)
Smoking Status	
Current	99 (18.61%)
Past	133 (25.00%)
Never	298 (56.01%)
Unknown	2 (0.38%)
Diagnosis	
CLE	372 (69.92%)
CLE + SLE	136 (25.56%)
DM	160 (30.08%)

CLE = Cutaneous Lupus Erythematosus

SLE = Systemic Lupus Erythematosus

DM = Dermatomyositis

Table II

Summary of Antimalarial Treatment Courses

Antimalarial Treatment	Number of Subject (%)n=532	Number of Courses	Average Duration Per Course (Months)	Average Duration Per Subject (Months)
HCQ	492 (92.5)	650	38.56	50.94
CQ	59 (11.1)	68	24.91	28.72
Q	63 (11.8)	71	16.88	19.02
HCQ-Q	228 (42.9)	287	32.26	40.61
CQ-Q	54 (10.2)	58	39.02	41.91

HCQ = hydroxychloroquine; CQ = chloroquine; Q = quinacrine; HCQ-Q = hydroxychloroquine + quinacrine; CQ-Q = chloroquine + quinacrine

Table III

Summary of Antimalarial Treatment Related Toxicities

Toxicity	Number of Events	Number of Patients n = 532 (%)
Dermatologic		
Cutaneous Eruption	65	61 (11.5)
Dyspigmentation ^a	26	26 (4.9)
Alopecia	8	7 (1.3)
Bleaching of hair	1	1 (0.2)
Gastrointestinal (GI)		
GI Upset ^b	40	38 (7.1)
Weight Loss	1	1 (0.2)
Weight Gain	1	1 (0.2)
Neurologic		
Dizziness	10	10 (1.9)
Headache	10	10 (1.9)
Ototoxicity ^e	8	5 (0.9)
Sleep Disturbances ^c	5	5 (0.9)
Mental Fog ^d	5	5 (0.9)
Peripheral Neuropathy	4	4 (0.8)
Tremors	2	2 (0.4)
Psychosis ^f	1	1 (0.2)
Retinal Toxicity^g	17	17 (3.2)
Musculoskeletal^h	7	7 (1.3)
Transaminitisⁱ	4	4 (0.8)
Cardiovascular^j	2	2 (0.4)
Respiratory^k	1	1 (0.2)
Hematologic^l	1	1 (0.2)
Other		
Constitutional Symptoms ^m	6	6 (1.1)
Metallic taste	4	4 (0.8)
Mood Disturbance/Irritability	4	4 (0.8)

* Some patients experienced multiple toxicities.

^a Blue-black or yellow discoloration of skin, mucous membranes, and/or nails;

^b Nausea/vomiting/diarrhea/constipation

^c Insomnia, lucid dreams, and nightmares

^d Mental slowing, memory problems, and poor concentration

^eTinnitus +/- hearing loss

^fAuditory hallucinations during accidental hydroxychloroquine overdose

^gTwo of these patients only reported subjective complaints of visual deficits; remainder had evidence of antimalarial induced retinal toxicity based on visual field testing.

^hSubjective complaints of arthralgia and myalgia

ⁱSeen in one patient after 1 month of HCQ; one patient after 2 years of HCQ-Q; two patient 3 months after Q added to long-term (25 years and 7 years) HCQ monotherapy

^jOne case of arrhythmia on chloroquine and one case of palpitations on hydroxychloroquine

^kSelf-limited chest-tightness and dyspnea for 20 minutes after taking hydroxychloroquine; unclear if due to antimalarial medication but hydroxychloroquine was discontinued

^lPancytopenia in setting of evolving myelodysplastic syndrome—unclear if due to antimalarial medication

^mLethargy and weakness

Table IV

Results from Cox proportional hazard models of toxicities on various antimalarial regimens in comparison with HCQ

Toxicity	Treatment Course	Hazard Ratio (HR) ^a	95% Simultaneous Confidence Interval for HR	p-value for HR
Skin Eruption				
	CQ	0.28	0.02–3.15	0.21
	Q	†		
	HCQ-Q	0.23	0.07–0.82	0.01
	CQ-Q	0.85	0.20–3.60	0.79
Dyspigmentation				
	CQ	†		
	Q	4.05	0.70–23.58	0.06
	HCQ-Q	1.52	0.38–6.11	0.47
	CQ-Q	1.30	1.10–16.72	0.81
GI Upset				
	CQ	0.35	0.03–5.13	0.31
	Q	1.14	0.27–9.94	0.83
	HCQ-Q	0.26	0.06–1.20	0.02
	CQ-Q	0.39	0.04–5.75	0.35
Neurologic				
	CQ	†		
	Q	0.46	0.04–5.41	0.45
	HCQ-Q	0.20	0.03–1.16	0.03
	CQ-Q	0.47	0.04–5.49	0.46
Ophthalmic				
	CQ	30.35	1.50–613.30	0.01
	Q	†		
	HCQ-Q	2.25	0.07–68.79	0.57
	CQ-Q	26.66	21.64–432.37	0.005

HCQ = hydroxychloroquine; CQ = chloroquine; Q = quinacrine; HCQ-Q = hydroxychloroquine + quinacrine; CQ-Q = chloroquine + quinacrine

^aHazard ratio adjusted for sex, age, race, and smoking status (never vs. current and past smokers)

†No observations of toxicity