HHS Public Access

Author manuscript

*J Am Acad Dermatol*. Author manuscript; available in PMC 2018 August 01.

Published in final edited form as:

*J Am Acad Dermatol*. 2017 August ; 77(2): 374–377. doi:10.1016/j.jaad.2017.03.027.

# The quinacrine experience in a population of cutaneous lupus erythematosus and dermatomyositis patients

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**Keywords**

Quinacrine; Hydroxychloroqine; Cutaneous Lupus Erythematosus; Dermatomyositis; FDA; Drug Compounding

## To the Editor

Quinacrine, a compounded antimalarial, has been used for patients intolerant or unresponsive to hydroxychloroquine. In March 2016 the Pharmacy Compounding Advisory Committee (PCAC) raised safety concerns about quinacrine-associated aplastic anemia. Additionally, the Office of New Drugs (OND) advised that although quinacrine may be safe at the 100 mg/day dose prescribed for rheumatic skin diseases, generalists might prescribe this drug at higher dosages and for alternative indications that have yet to be formally studied. Consequently, this orphan drug may no longer be compounded or might become effectively unavailable with prescription requiring an IND, IRB approval, patient consent, and toxicity reporting.[1]

To evaluate the need for continued access, we surveyed providers at various institutions to determine their quinacrine prescribing practices. Two rheumatologic skin disease specialists (Drs. MC and CB) from Texas, estimated having seen 96 and 30 patients on quinacrine within the last year but could not provide exact figures. An academic dermatologist (Dr. RDS) from Utah, prescribed quinacrine to 98 patients over a 3-year period (see acknowledgements). We examine the extent of quinacrine use and its associated toxicities at the Hospital of the University of Pennsylvania (HUP).

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**IRB Approval:** This study is exempt from IRB review.

**Conflict of Interest:** The authors have no conflict of interest to declare.

Through an electronic search of HUP's data stores from June 1st, 2015–May 31st, 2016, we found that out of 899,990 active patients 241 (0.027%) were prescribed quinacrine. Most prescriptions were ordered by dermatology (n=177) and rheumatology (n=75) with 18 individuals prescribed by multiple departments. Records from 111 patients who filled prescriptions at the hospital pharmacy indicate that quinacrine was prescribed to 63.1% (n=70) by dermatologists, 34.2% (n=38) by rheumatologists, and 2.7% (n=3) by internists. Although the OND stated that maintaining quinacrine availability would open access to "any prescriber…for any use…at any dose," we found that quinacrine has almost exclusively been prescribed by rheumatic skin disease specialists at our center.[1]

Secondly, we retrospectively analyzed two NIH-funded prospective longitudinal databases of cutaneous lupus erythematosus (CLE) (n=421) and dermatomyositis (DM) (n=215) initiated in 2007 by Dr. Victoria P. Werth's research team. All patients were seen at HUP's outpatient autoimmune skin disease clinic. Those without antimalarial history (n=73) or scant records (n=25) were excluded. Over half (58.7%, n=316) of the remaining 538 patients used quinacrine. Quinacrine users (n=314) were more likely to have smoking history (current=20.6%, past=28.8%, never=50%) than non-users (n=222, current=16.2%, past=19.4%, never=64.4%), $\chi^2$ (2, $N$=536) =10.79, p=0.0045, likely representing treatment escalations required in smokers (Table 1).[2]

Of the quinacrine users, 36 patients were started recently and details of the course are unavailable. Quinacrine was started in the majority (86.1%, n=241) of the remaining 280 due to hydroxychloroquine refractoriness, consistent with studies on its efficacy for recalcitrant disease.[3] Following initiation, quinacrine was discontinued in 50.4% (n=141), hydroxychloroquine in 44.5% (n=237), and chloroquine in 62.2% (n=61). Patients on these medications are not mutually exclusive as most were on either hydroxychloroquine or chloroquine in combination with quinacrine. Notably, quinacrine was discontinued more often than other antimalarials due to cost and access barriers (quinacrine: 23.4%, n=33; hydroxychloroquine: 4.6%, n=11; chloroquine: 16.4%, n=10) rather than side effects (quinacrine: 30.5%, n=43; hydroxychloroquine: 42.6%, n=101; chloroquine: 49.2%, n=30) (Table 2).

Following side effects, quinacrine was restarted in 27.7% (n=13), hydroxychloroquine in 25.7% (n=26), and chloroquine in 16.7% (n=5). There were two instances of mild transaminitis and three of slight hematological disturbances not clearly attributable to quinacrine. In prior reports of WWII soldiers, 1/500,000 patients experienced aplastic anemia at dosages exceeding 100 mg/day.[4,5] Quinacrine's safety is thus supported by our large experience.

Our study is limited by its retrospective methodology. It is crucial to continue to examine the repercussions of the loss of quinacrine availability considering the lack of suitable alternatives.

## Acknowledgments

We thank Drs. Richard Sontheimer, Melissa Costner, and Carolyn Bangert for providing information about their quinacrine prescribing practices. We are also grateful to Ms. Yuliya Borovskiy from the Penn DAC for her assistance with data acquisition and Dr. Andrew Cucchiara for his guidance with Redcap project planning.

**Funding Sources:** This work was supported by the United States Department of Veterans Affairs (Veterans Health Administration, Office of Research and Development and Biomedical Laboratory Research and Development) Merit Review 5 I01 BX000706-04 (PI: Werth) and by the United States Department of Health and Human Services and the National Institutes of Health (National Institute of Arthritis and Musculoskeletal and Skin Diseases) R21 AR066286 (PI: Werth).

## Abbreviations List

| | |
|---|---|
| **PCAC** | Pharmacy Compounding Advisory Committee |
| **OND** | Office of New Drugs |
| **IND** | Investigational New Drug |
| **IRB** | Institutional Review Board |
| **HUP** | Hospital of the University of Pennsylvania |
| **CLE** | Cutaneous Lupus Erythematosus |
| **SLE** | Systemic Lupus Erythematosus |
| **LP** | Lupus Profundus |
| **LET** | Lupus Erythematosus Tumidus |
| **SCLE** | Subacute Cutaneous Lupus Erythematosus |
| **ACLE** | Acute Cutaneous Lupus Erythematosus |
| **DM** | Dermatomyositis |
| **WWII** | World War II |
| **HCQ** | Hydroxychloroquine |
| **CQ** | Chloroquine |
| **N / V / D / C** | Nausea / Vomiting / Diarrhea / Constipation |
| **AST** | Aspartate Aminotransferase |
| **ALT** | Alanine Aminotransferase |
| **MDS** | Myelodysplastic Syndrome |

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## Table 1

Demographics of all patients on antimalarials and subset on quinacrine

| | Total on Antimalarials N = 538 N (%) | Quinacrine Users N = 316 N (%) | Percentage of Quinacrine Users per Demographic Category % |
|---|---|---|---|
| **Mean Age** | 52.3 | 52.9 | |
| **Gender** | | | |
| Female | 458 (85.1) | 273 (86.4) | 59.6 |
| Male | 80 (14.9) | 43 (13.6) | 53.8 |
| **Race** | | | |
| Black | 125 (23.2) | 76 (24.1) | 60.8 |
| White | 376 (69.9) | 217 (68.7) | 57.7 |
| Asian | 16 (3.0) | 7 (2.2) | 43.8 |
| Other | 18 (3.3) | 14 (4.4) | 77.8 |
| Unknown | 3 (0.6) | 2 (0.6) | 66.7 |
| **Ethnicity** | | | |
| Hispanic | 15 (2.8) | 10 (3.2) | 66.7 |
| Not-Hispanic | 519 (96.5) | 303 (95.9) | 58.4 |
| Unknown | 4 (0.7) | 3 (0.9) | 75 |
| **Smoking History** | | | |
| Never | 301 (55.9) | 158 (50) | 52.5 |
| Current | 101 (18.8) | 65 (20.6) | 64.4 * |
| Past | 134 (24.9) | 91 (28.8) | 67.9 * |
| Unknown | 2 (0.4) | 2 (0.6) | 100 |
| **Disease Type** | | | |
| CLE | 368 (68.4) | 222 (70.3) | 60.3 |
| Dermatomyositis | 170 (31.6) | 94 (29.7) | 55.3 |
| **CLE subtype** | | | |
| Discoid Total | 162 (30.1) | 114 (21.2) | 70.4 |
| Discoid + SLE | 64 (11.9) | 53 (16.8) | 84.7 |
| Discoid + LP | 6 (1.1) | 6 (1.9) | 100 |
| LET Total | 24 (4.5) | 12 (3.8) | 50 |
| LET +SLE | 1 (0.2) | 1 (0.3) | 100 |
| LP | 4 (0.7) | 1 (0.3) | 25 |
| Hypertrophic | 3 (0.6) | 2 (0.6) | 66.7 |
| Chilblains | 2 (0.4) | 2 (0.6) | 100 |
| Lupus Pernio | 1 (0.2) | 1 (0.3) | 100 |
| SCLE Total | 70 (16.9) | 41 (12.9) | 58.6 |
| SCLE + SLE | 19 (3.5) | 10 (3.2) | 52.6 |
| ACLE Total | 12 (2.2) | 4 (1.3) | 33.4 |

| | **Total on Antimalarials N = 538 N (%)** | **Quinacrine Users N = 316 N (%)** | **Percentage of Quinacrine Users per Demographic Category %** |
|---|---|---|---|
| ACLE + SLE | 11 (2.0) | 4 (1.3) | 36.7 |
| **Total SLE** | 64 (11.9) | 41 (13.0) | 64.1 |
| History of HCQ [a] | 534 (99.3) | 312 (98.7) | 58.4 |
| History of CQ [b] | 98 (18.2) | 85 (26.9) | 86.7 |

[*] Quinacrine users are significantly more likely to have smoking history than non-users, p = 0.0045.

[a] HCQ = hydroxychloroquine,

[b] CQ = Chloroquine

**Table 2**

Toxicities of quinacrine, hydroxychloroquine, and chloroquine

| | Quinacrine N (%) | HCQ * N (%) | CQ ** N (%) |
|---|---|---|---|
| **Total** | **43** | **101** | **30** |
| **Skin** | | | |
| Dyschromia | 8 (18.6) | 2 (2.0) | 0 |
| Pruritic Rash | 11 (25.6) | 36 (35.6) | 7 (23.4) |
| Bullous Rash | 0 | 2 (2.0) | 0 |
| CLE exacerbation | 0 | 1 (1.0) | 0 |
| Alopecia | 0 | 5 (5.0) | 3 (10.0) |
| **Gastrointestinal** | | | |
| N / V / D / C [a] | 8 (18.6) | 20 (19.8) | 6 (20.0) |
| Transaminitis | 2 (4.7) [b] | 1 (1.0) | 0 |
| Dysgeusia | 2 (4.7) | 0 | 1 (3.4) |
| **Neurologic** | | | |
| Headache / Dizziness | 3 (7.0) | 10 (9.9) | 1 (3.4) |
| Tinnitus | 1 (2.3) | 2 (2.0) | 0 |
| Hearing Loss | 0 | 1 (1.0) | 0 |
| Insomnia | 1 (2.3) | 0 | 1 (3.4) |
| Anxiety | 1 (2.3) | 0 | 0 |
| Mental Fog | 1 (2.3) | 3 (3.0) | 1 (3.4) |
| Auditory Hallucinations | 0 | 1 (1.0) [g] | 0 |
| Nightmares | 0 | 1 (1.0) | 0 |
| Ocular | 0 | 18 (17.8) | 10 (33.4) |
| **Musculoskeletal** | | | |
| Myopathy | 1 (2.3) | 1 (1.0) | 0 |
| Muscle Cramps | 0 | 1 (1.0) | 0 |
| Joint Pains | 0 | 1 (1.0) | 0 |
| Shakes / Tremors | 0 | 1 (1.0) | 0 |
| **Hematologic / Oncologic** | | | |
| Thrombocytopenia | 1 (2.3) [c] | 0 | 0 |
| Leukopenia | 1 (2.3) [d] | 0 | 0 |
| Pancytopenia | 1 (2.3) [e] | 0 | 0 |
| **Other** | | | |
| Hypersensitivity | 1 (2.3) [f] | 0 | 0 |
| Lethargy/Fatigue | 4 (9.3) | 1 (1.0) | 1 (3.4) |
| Weight Gain | 0 | 1 (1.0) | 0 |
| Palpitations | 0 | 1 (1.0) | 0 |

[a] Nausea / Vomiting / Diarrhea / Constipation

[b] Transaminitis was mild. Lab values are available for one case: AST 47 ALT 85

[c] Lab values unclear from records

[d] In setting of lupus flare in patient with SLE-related leukopenia; unclear if drug induced

[e] In the setting of evolving MDS. WBC 2.9, Hematocrit 31.7, Platelets 130K

[f] Dyspnea, body cramping, fatigue, methemoglobinemia; similar reaction on dapsone

[g] Related to supratherapeutic plaquenil dose

[*] HCQ = Hydroxychloroquine;

[**] CQ = Chloroquine