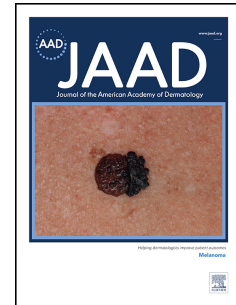


# Journal Pre-proof

Adverse Cutaneous Reactions Secondary to Hydroxychloroquine in Patients with Dermatomyositis, Lupus Erythematosus and Lichen Planopilaris

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PII: S0190-9622(21)00359-5

DOI: <https://doi.org/10.1016/j.jaad.2021.02.034>

Reference: YMJD 15703

To appear in: *Journal of the American Academy of Dermatology*

Received Date: 29 August 2020

Revised Date: 10 February 2021

Accepted Date: 12 February 2021

Please cite this article as: Akabane AL, Smith GP, Adverse Cutaneous Reactions Secondary to Hydroxychloroquine in Patients with Dermatomyositis, Lupus Erythematosus and Lichen Planopilaris, *Journal of the American Academy of Dermatology* (2021), doi: <https://doi.org/10.1016/j.jaad.2021.02.034>.

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**Article type:** Research Letter

**Title:** Adverse Cutaneous Reactions Secondary to Hydroxychloroquine in Patients with Dermatomyositis, Lupus Erythematosus and Lichen Planopilaris

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**Funding sources:** None

**Conflicts of Interest:** None declared.

IRB approval status: Reviewed and approved by Partners Human Research Committee; approval #2014P002301/MGH

**Reprint requests:** Andressa Akabane

**Manuscript word count:** 500 words [excluding capsule summary, references, tables]

**Abstract word count:** 0

**Capsule summary word count:** 0

**References:** 3

**Figures:** 0

**Tables:** 2

Supplementary tables: 0

**Keywords:** adverse cutaneous drug reactions; hydroxychloroquine; dermatomyositis; lupus erythematosus; lichen planopilaris; allergy

**Body of manuscript**

Studies comparing the frequency of adverse cutaneous reactions (ACR) secondary to hydroxychloroquine (HCQ) in patients with dermatomyositis (DM) and cutaneous lupus erythematosus (CLE) have shown mixed results. Callen et al and Wolstencraft et al, both found increased ACR in DM.<sup>1,2</sup> In contrast, Gonzalez et al did not find differences.<sup>3</sup> This study had two objectives: first, to evaluate if increased ACR exists in our DM patients and, secondly, to identify specific factors (e.g. history of atopy, other drug allergies, baseline eosinophilia) in patients who developed ACR to HCQ that might enable us to predict, and thereby avoid this reaction. For this latter purpose, we sought to increase our dataset by including patients with lichen planopilaris (LPP), as HCQ was also frequently prescribed to them by dermatologists in our institution.

Based on ICD-10 codes, 1163 patients with DM seen at Mass General Brigham outpatient dermatology clinics between January/2000 and December/2019 were identified. For inclusion, patients had to have the M-33 code recorded at least twice. Individual medical chart review was performed to confirm diagnosis and use of HCQ. This produced a dataset of DM patients who took 200-800 mg HCQ daily. Age and gender-matched CLE (n=271) and LPP (n=74) controls were then extracted in an identical manner for comparison to our DM dataset. After review, this provided 150 CLE and 36 LPP patients. Only cases of ACR diagnosed by a dermatologist, supported either clinically or by histopathologic confirmation, were included.

The overall incidence of ACR to HCQ was 4.2% (13/306) and was most frequent in DM ( $p < .001$ -Table I). This finding of increased incidence in patients with DM is consistent with Callen et al and Wolstencroft et al. However, only 9.2% of DM patients had ACR to HCQ, which was lower than reported by Callen et al (31%) and Wolstencroft et al (20.7%).<sup>1,2</sup> There were no statistically significant differences of daily HCQ dose based on actual or ideal body weight between DM patients with HCQ-induced ACR and those without it ( $p = .58$ ).

In contrast with our hypothesis that patients with DM may also have more non-HCQ drug allergies, these were more common in CLE patients ( $p=.009$ ). Specifically, hypersensitivity to sulfa was more common in CLE patients ( $p=.004$ ). Baseline eosinophilia was most frequent in LPP patients ( $p=.002$ ). Of those who presented with ACR to HCQ (Table II), those with a higher mean age were more likely to develop HCQ-associated ACR (56.1 vs. 46.6,  $p=.048$ ), but this lost significance when adjustment for multiple comparisons was performed.

In DM patients, those on immunosuppression were less likely to develop ACR to HCQ than those who were not ( $OR=0.18$ ,  $p=.02$ ). This is potentially clinically useful information as, if immunosuppressant use is protective, the addition of HCQ only after immunosuppression may help reduce the risk for allergy to HCQ. In conclusion, we did not identify statistically significant risk factors in patients with DM that would allow prediction of HCQ-induced ACR. While larger than previous studies, this study shares the limitation that it is retrospective and represents only a limited sample from a single institution.

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**Table legend**

Table I. "Patient Characteristics by Disease Type"

Table II. "Patient Characteristics by ACR Secondary to Hydroxychloroquine"

Table I. Patient Characteristics by Disease Type

| Variable                                             | DM (N= 120) | CLE (N= 150) | LPP (N= 36) | P Value            |
|------------------------------------------------------|-------------|--------------|-------------|--------------------|
| HCQ- ACR, No. (%)                                    | 11 (9.2)    | 0            | 2 (5)       | <.001 <sup>a</sup> |
| Additional drug allergy, No. (%)                     | 60 (50)     | 100 (66.7)   | 17 (47)     | .009 <sup>b</sup>  |
| Concomitant immunosuppression <sup>c</sup> , No. (%) | 74 (62)     | 55 (37)      | 3 (8)       | <.001 <sup>a</sup> |
| <b>Drug class, No. (%)</b>                           |             |              |             |                    |
| Sulfa                                                | 12 (10)     | 37 (24.7)    | 4 (11)      | .004 <sup>a</sup>  |
| Penicillin                                           | 20 (16.7)   | 33 (22)      | 8 (22)      | .22 <sup>a</sup>   |
| Opioid                                               | 3 (2.5)     | 10 (6.7)     | 3 (8)       | .14 <sup>a</sup>   |
| Iodinated contrast                                   | 1 (0.8)     | 7 (4.7)      | 0           | .12 <sup>a</sup>   |
| <b>Other, No. (%)</b>                                |             |              |             |                    |
| Atopic diseases                                      | 14 (11.7)   | 27 (18.1)    | 5 (13)      | .35 <sup>a</sup>   |
| Eosinophilia <sup>c</sup>                            | 1 (1.6)     | 1 (2.4)      | 4 (19)      | .002 <sup>a</sup>  |

<sup>a</sup> Fisher's exact test <sup>b</sup> Pearson chi-square test <sup>c</sup> Use of at least one immunosuppressant drug <sup>d</sup> Reported before HCQ exposure.

Abbreviations: DM, dermatomyositis, CLE, cutaneous lupus erythematosus, LPP, lichen planopilaris, HCQ, hydroxychloroquine, ACR, adverse cutaneous reaction

Table II. Patient Characteristics by ACR Secondary to Hydroxychloroquine

| Variable                              | No HCQ-ACR (N= 293) | HCQ- ACR (N= 13) | P Value           | Adjusted P value <sup>d</sup> |
|---------------------------------------|---------------------|------------------|-------------------|-------------------------------|
| Age, mean (SD), y                     | 46.6 (17)           | 56.1 (14)        | .048 <sup>a</sup> | .12                           |
| Male gender, No. (%)                  | 32 (10.9)           | 2 (13)           | .67 <sup>b</sup>  | .76                           |
| HCQ dose, No. (%)                     |                     |                  |                   |                               |
| ≥ 400 mg/d                            | 226 (79.9)          | 6 (66)           | .02 <sup>c</sup>  | .1                            |
| Number of immunosuppressants, No. (%) |                     |                  |                   |                               |
| 0                                     | 160 (54.6)          | 9 (69)           | .31 <sup>b</sup>  | .51                           |
| 1                                     | 84 (28.7)           | 1 (7)            |                   |                               |
| 2                                     | 43 (14.7)           | 3 (23)           |                   |                               |
| 3                                     | 6 (2)               | 0                |                   |                               |
| Other                                 |                     |                  |                   |                               |
| Smoking                               | 82 (29.1)           | 4 (33)           | .76 <sup>b</sup>  | .76                           |

<sup>a</sup> Two- sample *t* test <sup>b</sup> Fisher's exact test <sup>c</sup> Pearson chi-square test <sup>d</sup> False Discovered Rate (FDR) adjusted for multiple comparisons

Abbreviations: HCQ, hydroxychloroquine, ACR, adverse cutaneous reaction, SD, standard deviation