Characterizing the adverse dermatologic effects of hydroxychloroquine: A systematic review

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Background: Hydroxychloroquine is associated with myriad adverse dermatologic effects, most of which are poorly characterized by the literature, with unknown frequencies and risk factors.

Objective: To conduct a systematic review of the adverse dermatologic effects and predisposing factors of hydroxychloroquine toxicity.

Results: The review included 94 articles comprising 689 dermatologic adverse effects. A total of 21 unique dermatologic reactions were reported, most commonly drug eruption or rash (358 cases), cutaneous hyperpigmentation (116), pruritus (62), acute generalized exanthematous pustulosis (27), Stevens-Johnson syndrome or toxic epidermal necrolysis (26), hair loss (12), and stomatitis (11). Almost all underlying conditions were rheumatologic or autoimmune in nature, composed primarily of lupus erythematous (72% of all cases) and rheumatoid arthritis (14%). The range of reported mean cumulative dosages was wide, with some adverse reactions found after as little as 3 g or as much as 2500 g.

Limitations: Dermatologic adverse events and primary diagnoses related to the use of hydroxychloroquine may be under-reported as only case reports and clinical trials that reported at least 1 dermatologic adverse effect were included.

Conclusion: Although hydroxychloroquine is generally well tolerated, dermatologic adverse effects involving the skin, hair, or nails are a frequent and significant complication. Most of these reactions occurred after treatment of autoimmune conditions, often manifesting on the skin after a wide range of cumulative dosages. (J Am Acad Dermatol 2020;83:563-78.)

Key words: adverse effect; adverse event; antimalarial; autoimmune; dermatomyositis; drug eruption; drug rash; hydroxychloroquine; hyperpigmentation; lupus; Plaquenil; rheumatology.

First developed to treat malaria in 1955, hydroxychloroquine (Plaquenil; Sanofi, Bridgewater, NJ) has evolved to become a commonly used agent in the treatment of autoimmune diseases, especially those involving the skin. Recognition and monitoring of adverse effects is an important component in the use of this medication.

Although hydroxychloroquine is associated with myriad adverse dermatologic effects, most of these are poorly characterized in the literature, with unknown frequencies and risk factors. As the incidence of autoimmune and rheumatologic conditions increases,[1] dermatologists must be prepared to predict, identify, and manage the relevant adverse effects associated with frequent hydroxychloroquine use. Here we report the results of our systematic review of the evidence-based literature on the adverse dermatologic effects and possible predisposing factors of hydroxychloroquine toxicity.

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Funding sources: None.
Conflicts of interest: None disclosed.
IRB approval status: Exempt from review.
Accepted for publication April 4, 2020.
Reprints not available from the authors.

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Published online April 11, 2020.
0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2020.04.024

METHODS

A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The PubMed and Cochrane databases were searched on November 30 and 31, 2019, for all peer reviewed articles published until December 2019 using the following search terms entered in separate pairs: "hydroxychloroquine *or* Plaquenil" *and* "adverse effects." Only articles in English concerning the study of hydroxychloroquine in humans were included. Case studies, case series, prospective and retrospective studies, and clinical trials that recorded cases of dermatologic adverse effects after hydroxychloroquine use were retrieved. Review articles, articles unavailable to the study team, letters to the editor, and clinical trial proposals were excluded. After full-text review, studies that did not specify hydroxychloroquine as the cause of a particular adverse event were excluded (ie, Mittal[2] 2018). Study design, patient, and outcome data were extracted and summarized from each article (Table I).[3-97]

CAPSULE SUMMARY

- The myriad adverse dermatologic effects of hydroxychloroquine are historically poorly characterized, with unknown frequencies and risk factors.
- The most common reactions included drug eruptions, hyperpigmentation, pruritus, and acute generalized exanthematous pustulosis, occurring over a wide range of mean cumulative doses. Almost all underlying conditions were rheumatologic or autoimmune in nature.

RESULTS

Study selection

The search strategy revealed 1163 records after duplicates were removed. Articles were screened by title, abstract, and full text as needed to determine eligibility. After the initial screening, 139 full-text articles were assessed for final inclusion. The bibliographic evaluation identified 2 additional records, resulting in 94 articles included in this review. Of these inclusions, 9 were randomized controlled trials, 20 were retrospective studies, 2 were prospective or cross-sectional studies, and 63 were case studies or series. The selection process of these included articles and their corresponding levels of evidence according to the Oxford Centre for Evidence-based Medicine were recorded (Fig 1; Table I).

Overall results

There were 689 reported cases of adverse dermatologic effects caused by hydroxychloroquine (Table II). This number and subsequent data are derived only from studies that reported an adverse dermatologic reaction to hydroxychloroquine.

Of the total 689 cases, 592 were reported as part of a large clinical trial or study, and 97 were reported independently as case studies or case series. There were 21 unique dermatologic reactions reported, with 8 of these reactions reported at least 10 times, including drug eruption or rash, cutaneous hyperpigmentation, pruritus, Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP), psoriasis, hair loss, and stomatitis. An additional 2 studies reported 30 adverse dermatologic reactions but did not specify the exact details of these reactions.[12,18]

The 94 articles consisted of 3578 patients, 83% of whom were female and aged older than 50 years. The largest randomized controlled study included in this review involved 845 patients.[82]

The conditions for which hydroxychloroquine was used as treatment were almost all autoimmune or rheumatologic in etiology (Fig 2). The underlying diseases for which dermatologic adverse events were recorded, in order of decreasing frequency, consisted of lupus erythematosus (systemic lupus erythematosus and discoid lupus erythematosus), rheumatoid arthritis (RA), dermatomyositis, unspecified/unknown rheumatologic conditions, Sjögren syndrome, osteoarthritis, refractory chronic urticaria, polymorphic light eruption, psoriasis, seronegative arthritis, morphea, and polymyalgia rheumatica. Diseases reported by only 1 case report each were lichen planopilaris, leukocytoclastic vasculitis, Crohn's disease, arthralgia, and ankylosing spondylitis.

The approximate average cumulative dose of hydroxychloroquine given (dosage per day × approximate number of days) was estimated for each case (Table II). When available, the range of doses precipitating each adverse effect was listed. Almost all adverse dermatologic effects were found on the skin, but unwanted changes of the mucosa, hair, and nails were diagnosed as well.

Skin

An adverse reaction arising on the skin was reported in 94.4% of all cases. Drug eruptions were the most common adverse effect (358 cases), followed by hyperpigmentation (116), pruritus (62), SJS/TEN (26), and AGEP (27). More rare

Abbreviations used:

AGEP: acute generalized exanthematous pustulosis
RA: rheumatoid arthritis
SJS: Stevens-Johnson syndrome
TEN: toxic epidermal necrolysis

unwanted effects included photosensitivity/photodermatitis, urticaria, psoriasis, drug reaction with eosinophilia and systemic symptoms, erythroderma, blistering, erythema multiforme, porphyria, Sweet syndrome, and erythema annulare centrifugum. The 2 studies that did not elucidate which adverse dermatologic effects were observed reported an unknown number of eruption, pruritus, hyperpigmentation, and flushing reactions.[12,18]

Detailed accounts of the drug eruptions associated with hydroxychloroquine were rare, but most often were depicted as maculopapular, erythematous, and urticarial. The exact clinical descriptions, dosing, time to rash development, and resolution course were recorded for all studies reporting a hydroxychloroquine drug eruption (Table III).* All hyperpigmentation reactions were described as blue-gray discoloration. These changes were observed on nearly all locations of the face and body, with 1 individual displaying a serpentine supravenous presentation.[62] Psoriasiform adverse reactions were diagnosed as inverse, pustular, or erythrodermic, when specified.

The mean cumulative dosages associated with these reactions varied. Five different reactions were associated with a mean cumulative dose exceeding 100 g: SJS/TEN (913 g), pruritus (823 g), drug eruption (537 g), hyperpigmentation (452 g), and photosensitivity/photodermatitis (150 g). The range of reported mean cumulative dosages was wide, with some adverse reactions found after as little as 3 g or as much as 2500 g. One of the most common adverse effects, AGEP, occurred after an average cumulative dose of only 4 g.

Hair

Adverse reactions of the hair were reported in 17 patients (2.9% of all cases). Hair loss was diagnosed most frequently (12 patients), occurring after a mean cumulative dose of 105 g (range, 67-150 g). Hyperpigmentation and bleaching of the hair were comparatively much rarer, with only 4 cases and 1 case observed, respectively.

Mucosa

Mucosal ulceration (stomatitis) was the most common adverse mucosal effect associated with hydroxychloroquine. Reported only 11 times, this reaction developed after a mean cumulative dose of 124 g (range, 72-150 g). Mucosal hyperpigmentation was reported 7 times, developing after a mean dose of 421 g (range, 361-720 g).

Nails

Melanonychia was observed in 3 patients after hydroxychloroquine use, occurring after a mean cumulative dose of 230 g (range, 198-261 g).

DISCUSSION

This study reveals that hydroxychloroquine may provoke numerous adverse dermatologic effects of varying severity. Although some reactions have been well established in the published literature, this systematic review uniquely characterizes the range of conditions reported with hydroxychloroquine and the possible risk factors for their development.

The epidemiology of our entire study cohort and subgroup composed of those experiencing adverse effects revealed a preponderance of female patients and older adults. Our data set mimics national trends of rheumatologic and autoimmune diseases, perhaps arguing against sex, age, and underlying disease as independent risk factors for dermatologic adverse effects with hydroxychloroquine. Although some research has proposed a possible ethnic difference in response to disease-modifying drugs, further study into the existence of polymorphic traits is needed before conclusions can be drawn.[98]

The most common dermatologic adverse effects with hydroxychloroquine—drug eruptions or rashes—were most often described as maculopapular, erythematous, or pruritic (Table III). These reactions tended to be mild, although many studies did not describe the morphologic or clinical presentation in detail. Gastrointestinal symptoms were reported in some patients.[83,90] Most of the drug eruptions occurred within 4 weeks of initiating hydroxychloroquine and disappeared within weeks of discontinuation, although reported ranges existed up to 95 weeks. Aside from abrupt discontinuation, hydroxychloroquine desensitization protocols, readministration at lower dosing, or switching to a different antimalarial were all successful management strategies in multiple patients. When treatment was required, oral and topical steroids were most frequently implemented.

*References 2,4,5,10,16,18,19,22,24,48,60,70,71,80-84,86,91,92,94,96,97

Table I. Reported cases of adverse dermatologic effects of hydroxychloroquine

Year	First author	Study design	LOE	Sample size	Age (±SD), y	Sex: F, M (%)	Underlying condition (% if specified)	Body part	Adverse reaction (% of sample size)	Approximate cumulative dose (g)
1983	Baler[3]	Case report	4	1	…	…	SLE	Skin	Porphyria	…
1983	Bell[4]	Retrospective cohort	2	108	53	55, 45	RA	Skin	Unspecified eruption (6.5) Hyperpigmentation (3.7)	…
1984	Bird[5]	RCT	1	20	50	75, 25	RA	Skin	Unspecified eruption (50) Pruritus (25) Stomatitis (25)	135
1985	Hudson[6]	Case report	4	1	…	…	…	Skin	Erythema annulare centrifugum	…
1985	Slagel[7]	Case report	4	1	31	100, 0	Psoriasis	Skin	Erythroderma (face, arms, trunk)	4.4
1987	Friedman[8]	Case report	4	1	60	0, 100	RA	Skin	Psoriasis (pustular)	8.4
1992	Sayers[9]	Retrospective case-control	2	31	…	…	Psoriatic arthritis	Skin	Psoriasis (6.5) (exacerbation)	…
1992	Clark[10]	RCT	1	65	39	94, 6	RA	Skin, hair	Unspecified eruption (3) Hair loss (3) Pruritus (3) Hyperpigmentation (2)	67.2
1994	Kutz[11]	Case report	4	1	36	100, 0	SLE	Skin	Porphyria cutanea tarda	2.8
1995	Esdaile[12]	RCT	1	60	53 ± 13	76, 24	RA	Skin	Unspecified adverse effect (16.6) (rash, pruritus, hyperpigmentation, flushing)	100
1996	Assier-Bonnet[13]	Case report	4	1	36	100, 0	Seronegative arthritis	Skin	AGEP	2.4
1996	Vine[14]	Case report	4	1	38	100, 0	Arthralgia	Skin	Psoriasis (pustular)	4.2
1998	Jimenez-Alonso[15]	Retrospective case-control	2	4	46	100, 0	SLE	Skin	Pruritus (aquagenic type)	72-1300
1998	Avina-Zubieta[16]	Retrospective cohort	2	401	49 ± 16	79, 21	RA (68) SLE (16) PA (9) Other (7)	Skin	Unspecified eruption (2)	…
1999	Holme[17]	Case report	4	1	22	100, 0	SLE	Skin	Pruritus	6
1999	Furst[18]	RCT	1	212	49 ± 12	75, 25	RA	Skin	Unspecified adverse effect (9.4)	67-201

2000	van Jaarsveld[19]	RCT	1	120	…	…	RA	Skin, mucosa, hair	Unspecified eruption (8.3) Stomatitis (0.8) Hair loss (0.8) Pruritus (0.8) Photosensitivity (0.8)	150
2001	Murphy[20]	Case report	4	1	39	100, 0	RA	Skin	TEN	5.6
2002	True[21]	Case report	4	1	…	0, 100	RA	Skin, mucosa	Hyperpigmentation (extremity, torso, hairline)	…
2002	Pelle[22]	Retrospective case-control	2	81	48*				Morbilliform eruption (13.6) Erythroderma (1.2) SJS (1.2) Unspecified eruption (2.4)	
2002	Leckie[23]	Case report	4	1	65				SJS	5.6
2002	Salido[24]	Retrospective cohort	2	11	49	100, 0	SLE, DLE, APS, SS	Skin	Unspecified eruption (82) Hyperpigmentation (9) Blisters (9)	1-6
2004	Evans[25]	Case report	4	1	28	100, 0	SLE	Skin	AGEP	5.6
2004	Millard[26]	Case report	4	1	48	100, 0	RA	Skin	Hyperpigmentation (gray) (face, trunk, thigh)	108
2004	Lisi[27]	Case report	4	1	74	0, 100	RA	Skin	Photodermatitis	…
2004	Welsch[28]	Case report	4	1	…	100, 0	Leukocytoclastic vasculitis	Skin	Psoriasis (pustular)	…
2006	Perez-Ezquerra[29]	Case report	4	1	47	100, 0	Ankylosing spondylitis	Skin	Erythema multiforme Contact dermatitis	…
2006	Reynaert[30]	Case report	4	1	…	100, 0	SLE	Skin	Hyperpigmentation (blue/gray) (pretibial, face)	…
2006	Ghaffarpour[31]	Case report	4	1	52	100, 0	RA	Skin	Pemphigus vulgaris	…
2007	Sidoroff[32]	Retrospective case-control	2	7	56 ± 21	86, 14	…	Skin	AGEP	…
2007	Volpe[33]	Case report	4	1	62	0, 100	Seronegative arthritis	Skin	DRESS	5.6
2007	Amichai[34]	Case report	4	1	37	100, 0	RA	Skin	Hyperpigmentation (blue/gray) (thighs)	144
2008	Paradisi[35]	Case series	4	3	36; 70; 79	67, 33	RA, SS; RA; PR	Skin	AGEP	4.2
2008	Pareek[36]	RCT	1	63	38	43, 57	Polymorphic light eruption	Skin	Hyperpigmentation (7.9)	18

Continued

Table I. Cont'd

Year	First author	Study design	LOE	Sample size	Age (±SD), y	Sex: F, M (%)	Underlying condition (% if specified)	Body part	Adverse reaction (% of sample size)	Approximate cumulative dose (g)
2008	Melikoglu[37]	Case report	4	1	48	100, 0	SS	Skin	Hyperpigmentation (blue/gray) (dorsal hands)	228
2008	Puri[38]	Case series	4	2	50; 78	100, 0	Undifferentiated arthritis; SLE and RNA	Skin	Hyperpigmentation (gray; blue) (upper back, shoulders; temple)	…
2008	Rood[39]	Case report	4	1	92	100, 0	RA	Skin	Hyperpigmentation (gray)	72
2008	Callaly[40]	Case report	4	1	29	100, 0	SS	Skin	TEN	432
2008	Meller[41]	Case report	4	1	25	100, 0	SLE	Hair	Bleaching	48
2009	Di Lernia[42]	Case report	4	1	63	100, 0	RA	Skin	AGEP	4
2009	Avram[43]	Case report	4	1	79	100, 0	RA	Skin	AGEP	…
2009	Lateef[44]	Case report	4	1	67	100, 0	SLE	Skin	AGEP TEN	…
2009	Morrison[45]	Case report	4	1	67	100, 0	SLE	Skin	Hyperpigmentation (blue/gray) (shins, forearms, hands)	84
2010	Park[46]	Case report	4	1	38	100, 0	DM	Skin	AGEP	4.2
2012	Cho[47]	Case report	4	1	58	100, 0	RA	Skin	Hyperpigmentation (blue/gray)	288
2012	Mittal[48]	Retrospective cohort	2	444	40 ± 13	85, 15	RA	Skin	Unspecified eruption (0.4)	…
2013	Bailey[49]	Case report	4	1	48	100, 0	SLE	Skin	AGEP	2.8
2013	Sifuentes[50]	Case report	4	1	…	…	SLE	Skin, Nails	Hyperpigmentation Melanonychia	…
2013	Jallouli[51]	Retrospective case-control	2	24	34 ± 13	96, 4	SLE	Skin	Hyperpigmentation	720
2013	Mir[52]	Case report	4	1	57	100, 0	SLE	Skin	Hyperpigmentation (blue/gray) (face, upper back, feet)	…
2013	Cohen[53]	Case report	4	1	66	100, 0	SLE	Skin	Hyperpigmentation (face, upper back, upper chest)	4300
2013	Tracy[54]	Case report	4	1	48	100, 0	SLE	Skin	Hyperpigmentation (gray)	2500
2014	Cameron[55]	Case report	4	1	30	100, 0	SLE	Skin	TEN	…

2015	Charfi[56]	Case report	4	1	33	100, 0	SLE	Skin	AGEP	3.4
2015	Zhang[57]	Case report	4	1	60	100, 0	SS	Skin	AGEP	4.2
2015	Sawalha[58]	Case report	4	1	32	100, 0	RA	Skin	Hyperpigmentation (black/gray)	36
2015	McCoy[59]	Case report	4	1	57	100, 0	SS	Skin	Psoriasis	…
2015	Soria[60]	Retrospective cohort	2	20	46	75, 25	SLE (30) RA (15) SS (15) Other (40)	Skin	Unspecified eruption (35) AGEP (30) Photosensitivity (15) Urticaria (10) DRESS (10)	…
2016	Pearson[61]	Case report	4	1	50	100, 0	RA	Skin	AGEP	5.6
2016	Lau[62]	Case report	4	1	53	0, 100	Idiopathic rheumatologic condition	Skin	Hyperpigmentation (serpentine supravenous)	…
2017	Duman[63]	Case report	4	1	21	100, 0	RA	Skin	AGEP	4.2
2017	Castner[64]	Case report	4	1	1	100, 0	SS	Skin	AGEP	…
2017	Pai[65]	Case report	4	1	50	100, 0	SLE	Skin	Erythroderma	…
2017	Boonpiyathod[66]	RCT	1	24	33 ± 12	88, 12	Refractory chronic urticaria	Skin	Hyperpigmentation (16.7)	33.6
2017	Bahloul[67]	Cross-sectional	2	41	39 ± 15	93, 7	SLE	Skin, Mucosa, Nail	Hyperpigmentation (51) (skin) Hyperpigmentation (12) (mucus) Hyperpigmentation (2.5) (nail)	361
2017	Coulombe[68]	Case report	4	1	48	0, 100	SLE	Skin	Hyperpigmentation (blue/gray)	…
2017	Yokogawa[69]	RCT	1	77	43 ± 13	74, 26	SLE	Skin	SJS (1.3) TEN (2.6) Generalized rash (2.6)	22.4-44.8
2017	Seth[70]	Retrospective cohort	2	45	44	77, 23	Refractory chronic urticaria	Skin	Unspecified eruption (2.2) Pruritus (2.2)	110
2017	Lee[71]	RCT	1	98	58 ± 8	86, 14	OA (hand)	Skin	Unspecified eruption (4) Pruritus (4)	2016
2017	Nic Dhonncha[72]	Retrospective cohort	2	27	56	93, 7	LPP	Skin	Urticaria (3.7)	20g
2018	Abou Assalie[73]	Case report	4	1	25	100, 0	SLE	Skin	Erythema multiforme	4.8g
2018	Ivo[74]	Case report	4	1	80s	100, 0	SS	Skin	Hyperpigmentation (black macules)	1584
2018	Thakur[75]	Case report	4	1	Elderly	100, 0	Granuloma annulare	Skin	Hyperpigmentation (blue/gray)	36

Continued

Table I. Cont'd

Year	First author	Study design	LOE	Sample size	Age (±SD), y	Sex: F, M (%)	Underlying condition (% if specified)	Body part	Adverse reaction (% of sample size)	Approximate cumulative dose (g)
2018	Tosios[76]	Case report	4	1	53	100, 0	RA	Skin, Mucosa	Hyperpigmentation (blue/gray)	720
2018	Wang[77]	Case report	4	1	41	100, 0	SLE	Skin	Psoriasis (erythrodermic)	24
2018	Darwin[78]	Case report	4	1	56	100, 0	Crohn's disease	Skin	Psoriasis (inverse)	72
2018	Ullah[79]	Case report	4	1	65	100, 0	RA	Skin	Psoriasis (inverse)	…
2018	Randhawa[80]	Case report	4	1	63	0, 100	RA	Skin	Unspecified eruption	…
2018	Chasset[81]	Retrospective cohort	2	64	38	81, 19	SLE	Skin	Unspecified eruption (12.5) (maculopapular erythema) Pruritus (12.5)	504
2018	Spinelli[82]	Retrospective cohort	2	845	46 ± 12	89, 11	SLE (76) DLE (24)	Skin	Unspecified eruption (20.4) Pruritus (4.1) Hyperpigmentation (4.1) SJS (2.0)	1000
2018	Kishi[83]	Retrospective cohort	2	31	45	84, 16	SLE	Skin	Unspecified eruption (66.7) (maculopapular erythema and urticaria)	…
2018	Matsuda[84]	Case report	4	1	36	100, 0	SLE	Skin	Unspecified eruption (erythematous, maculopapular)	2.8
2018	Tekgöz[85]	Case report	4	1	60	0, 100	RA	Skin	Hyperpigmentation (ochronosis)	146
2018	Wolstencroft[86]	Retrospective cohort	2	111	49	87, 13	DM	Skin	Unspecified eruption (20.7)	…
2019	Liccioli[87]	Case report	4	1	9	100, 0	SS	Skin	AGEP	3
2019	Girijala[88]	Case report	4	1	56	100, 0	SS	Skin	DRESS	…
2019	Kumar[89]	Retrospective cohort	2	84	30	77, 23	Morphea	Skin	Hyperpigmentation (2.4)	144
2019	Zhang[90]	Case report	4	1	55	100, 0	SLE	Nails	Melanonychia	198
2019	Miyagawa[91]	Prospective cohort	2	44	41 ± 12	89, 11	SLE	Skin, Hair, Mucosa	Unspecified eruption (47.7) Hair loss (20.5) Stomatitis (11.4) Pruritus (2.3)	72-144
2019	Takamasu[92]	Retrospective cohort	2	302	41 ± 15	88, 12	SLE	Skin	Unspecified eruption (8.3)	146

2019	Shindo[93]	Case report	4	1	34	100, 0	SLE	Skin	Psoriasis (pustular)	4.2
2019	Ototake[94]	Retrospective cohort	2	35	44 ± 17	72,28	SLE	Skin	Unspecified eruption (82.8)	4.2-6.3
2019	Manzo[95]	Case report	4	1	72	100, 0	SS	Skin	Sweet syndrome	5.6
2019	Barailler[96]	Case report	4	1	82	0, 100	SLE	Skin	Unspecified eruption	0.4
2019	Tal[97]	Retrospective cohort	2	13	51	92, 8	SLE (69) SS (8) RA (15) PR (8)	Skin	Unspecified eruption (100)	…

AGEP, Acute generalized exanthematous pustulosis; *APS*, antiphospholipid syndrome; *DLE*, discoid lupus erythematosus; *DM*, dermatomyositis; *DRESS*, drug reaction with eosinophilia and systemic symptoms; *EM*, erythema multiforme; *F*, female; *LOE*, level of evidence; *LPP*, lichen planopilaris *M*, male; *OA*, osteoarthritis; *PA*, palindromic arthritis; *PR*, polymyalgia rheumatica; *RA*, rheumatoid arthritis; *RCT*, randomized control trial; *SJS*, Stevens-Johnson syndrome; *SLE*, systemic lupus erythematosus; *SS*, Sjögren syndrome; *TEN*, toxic epidermal necrolysis.
*3 juvenile cases were not included in calculation.

Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

Historically, drug eruptions have been more commonly reported in patients with dermatomyositis than with lupus erythematosus,[22] although a lack of consensus exists in the published literature. A recent retrospective study comparing the frequency of adverse cutaneous drug eruptions in certain conditions found no significant difference between dermatomyositis and lupus (5% and 4%, respectively).[99] However, a different single-institutional study found that a hydroxychloroquine-associated skin eruption developed in 20.7% of patients with dermatomyositis.[86]

In our review, only 35 cases of drug eruptions were found in those with dermatomyositis, whereas 306 were found in those with lupus. The reason for our low case numbers may simply be a reflection of the disease prevalence of dermatomyositis. Given that more patients with RA or lupus were treated than patients with dermatomyositis, one would expect to find a higher overall number of adverse effects in the RA or lupus group.[100] In addition, we speculate that the range of adverse effects observed after hydroxychloroquine use in patients with dermatomyositis may consist of more nondermatologic

Table II. Reported adverse dermatologic effects of hydroxychloroquine

Adverse effect	Reported cases, No.	Cumulative dose, mean (range), g
Skin		
Drug rash/eruption	358	537 (3-2016)
Hyperpigmentation	116	452 (18-2500)
Pruritus	62	823 (6-2016)
SJS/TEN	26	913 (6-1000)
AGEP	27	4 (2-6)
Psoriasis	10	27
Photosensitivity	5	150
Urticaria	3	20
DRESS	5	6
Erythroderma	3	4
Blistering	2	3 (1-6)
Erythema multiforme	2	5
Sweet syndrome	1	6
Erythema annulare centrifugum	1	…
Unspecified adverse reaction	30	…
Hair		
Loss	12	105 (67-150)
Hyperpigmentation	4	67
Bleaching	1	48
Nails		
Melanonychia	3	230 (198-261)
Mucosa		
Stomatitis	11	124 (72-150)
Hyperpigmentation	7	421 (361-720)

AGEP, Acute generalized exanthematous pustulosis; *DRESS*, drug reaction with eosinophilia and systemic symptoms; *SJS*, Stevens-Johnson syndrome; *TEN*, toxic epidermal necrolysis.

adverse effects than dermatologic adverse effects, especially when compared with patients with RA or lupus. Other possible explanations for variations in rash susceptibility include variations in the chemical compositions of generic hydroxychloroquine formulations as well as differences in dermatomyositis-specific autoantibody profiles more prevalent in certain ethnicities or geographic regions.[99]

The different dermatologic reactions caused by hydroxychloroquine can be categorized in low or high average cumulative dose categories. Those occurring after a mean cumulative dose of greater than 100 g (high) included SJS/TEN, pruritus, drug eruption, cutaneous hyperpigmentation, melanonychia, photosensitivity, stomatitis, and hair loss. Those occurring after a mean cumulative dose of less than 100 g (low) included AGEP, urticaria, psoriasis, drug reaction with eosinophilia and systemic symptoms, erythroderma, blistering, erythema multiforme, porphyria, and hair hyperpigmentation.

Generally, adverse effects resulting from high mean cumulative doses were also reported most frequently; the 4 most common skin adverse effects all occurred with a mean cumulative dose of greater than 400 g. These average cumulative dose results mirror what is frequently seen clinically. AGEP often arises within days of drug exposure, self-resolving in only a few weeks; thus, it is reasonable to expect a low cumulative dose. Hyperpigmentation develops most commonly after long-standing use ranging from months to years, reflected by its high average cumulative dose.[51] Similarly, SJS/TEN can develop classically within 4 weeks of drug initiation, resulting in a wide range and high peak of average cumulative dose.

It is important to note that the mean cumulative dose ranges for each reported condition, particularly those concerning rarer diagnoses, are limited by small sample sizes, inconsistent recording, and wide ranges. We are therefore unable to draw any accurate conclusions based on the variable reporting. Whereas overall certain reactions are more likely to occur after prolonged treatment, dermatologists must be aware of the potential for these reactions to develop even after short courses.

The pathogeneses of each cutaneous reaction are not completely understood; however, recent research has revealed potential explanations. Hyperpigmentation, one of the most consistent and characteristic adverse effect, may be secondary to bruising, because significantly increased concentrations of iron and melanin can be seen in ecchymotic areas.[51] In support, 1 retrospective cohort study found 96% of those with hydroxychloroquine-induced hyperpigmentation had a condition predisposing them to bruising, most often an oral anticoagulation or antiplatelet regimen.[51] Histologic confirmation revealed increased superficial dermal deposition of iron in the hyperpigmented skin vs normal skin, a difference that may induce activation of melanocytes due to high hemosiderin content.[51,67] Our results revealed hyperpigmentation arising after a mean cumulative dose of 452 g, often occurring after months or years of treatment.

For RA and lupus erythematosus, dose-loading with hydroxychloroquine has been shown to improve the rate of response, logically resulting in numerically more adverse events among patients taking higher doses.[18,101] However, because the range of implicating doses in our study was extremely wide, it would be inaccurate to assume a strict dose-dependent relationship with hyperpigmentation.[51]

With psoriasis development or exacerbation, hydroxychloroquine causes enhanced and irregular keratinization in the upper epidermis, a stimulus thought to induce psoriasiform hyperplasia.[102] Up to

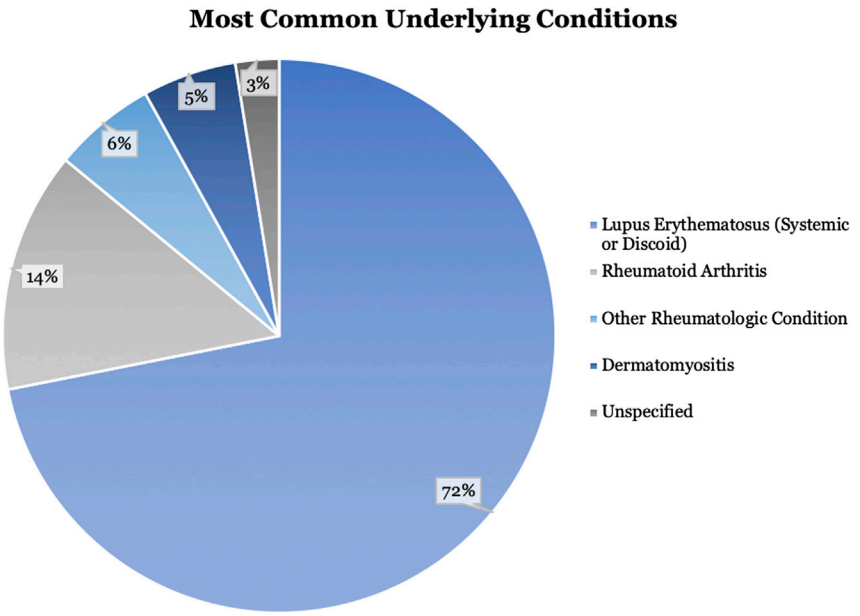

Fig 2. Most common underlying conditions among those experiencing adverse dermatologic reactions to hydroxychloroquine.

31% of patients with psoriasis have been reported to experience an exacerbation after treatment with synthetic antimalarial drugs; however, a recent systematic review reported a lack of high-quality evidence supporting a causal relationship.[7,103]

Two studies that reported hydroxychloroquine-induced porphyria were more accurately characterized as precipitating an underlying porphyria rather than causing a new diagnosis.[3,11] The proposed mechanism of action involves increased solubility of the drug-porphyrin complex, heightening the mobilization of porphyrins from the liver, and exacerbating symptoms that may have previously been subclinical. The mechanisms of hydroxychloroquine hair- and nail-related changes remain unknown.

Symptoms for most of the adverse effects reported in this study self-resolved after discontinuation of hydroxychloroquine within weeks to months. When additional agents were required, topical steroidal agents were the most common form of adjunctive treatment. With the life-threatening developments of SJS/TEN, only 2 deaths were reported, as other reports did not specify treatment regimen or outcome,[20,55]

This study has some limitations. Given the focus of the review, only case reports and clinical trials that reported at least 1 dermatologic adverse effect were included. For this reason, there may be an under-reporting of dermatologic adverse events and primary diagnoses related to the use of hydroxychloroquine. For example, a number of studies likely exist that have described long-term hydroxychloroquine use with no reported dermatologic adverse effects. In other cases (eg, Bahloul et al[67]), a lack of reported patient details or photographs made it difficult to determine whether hydroxychloroquine was the true cause of certain adverse events, leading to a possible overestimation of hydroxychloroquine-related adverse events in these studies. Similarly, many trials may have observed unwanted cutaneous effects but did not report them if their primary outcome was of an unrelated system (eg, cardiovascular, ocular). Thus, we could not estimate an incidence and prevalence of hydroxychloroquine-associated dermatologic toxicity, data that still remain undetermined.

Furthermore, creating accurate estimations of the percentage of patients with certain rheumatologic conditions who may experience adverse dermatologic events was difficult. Many large studies consisting of cohorts with multiple underlying conditions did not divide the total number of dermatologic adverse cases by the underlying condition. Consequently, it was not possible to conclude how likely a patient with a certain condition (ie, systemic lupus erythematosus) was to experience an adverse dermatologic reaction to hydroxychloroquine.

In addition, studies reporting multiple adverse effects often tallied these adverse effects separately. How many patients with dermatologic adverse effects also experienced systemic symptoms was unclear.

Table III. Characterizations of the drug eruptions with hydroxychloroquine

Year	First author	Description of skin eruption and systemic symptoms	Dosage, mg/d	Time to adverse effect	Resolution/treatment
1983	Bell[4]	No details	200-400	No details	15/17 patients required discontinuation
1984	Bird[5]	No details	400	No details	3/20 required discontinuation, resolution 6-45 weeks after treatment
1992	Clark[10]	No details	400	No details	No discontinuation
1998	Avina-Zubieta[16]	No details	400	No details	Unspecified number of those with skin rashes discontinued drug and switched to different antimalarial
1999	Furst[18]	No details	400-1200	0-24 weeks	No discontinuation
2000	van Jaarsveld[19]	No details	200-400	9-95 weeks	No discontinuation
2002	Pelle[22]	Generalized morbilliform, pruritic eruptions	200-400	≤3 weeks	All discontinued, unspecified number treated with tapering courses of oral prednisone
2002	Salido[24]	Mild rash throughout body and face, occasional blistering	Unspecified	0-30 days	Disappeared after discontinuation
2012	Mittal[48]	No details	Unspecified	≤6 months	Disappeared after discontinuation
2015	Soria[60]	Maculopapular exanthema	Unspecified	0-30 days	Disappeared after discontinuation (1-18 days)
2017	Seth[70]	Pruritus and rash	402	No details	Disappeared after discontinuation
2017	Lee[71]	Pruritus and rash	400	≤24 weeks	6/8 required discontinuation
2018	Randhawa[80]	Hypersensitivity, widespread skin eruption	Unspecified	2 weeks	Discontinuation, oral and topical steroids
2018	Wolstencroft[86]	Nonspecific, diffuse, erythematous, and pruritic symptoms. Systemic symptoms of muscle weakness, peripheral edema, gastrointestinal symptoms	200-800	≤4 weeks	Disappeared after discontinuation
2018	Mittal[2]	No details	200-400	No details	Discontinuation
2018	Chasset[81]	Maculopapular erythema	200-400	10-15 days	Discontinuation, switch to chloroquine well-tolerated
2018	Kishi[83]	Maculopapular erythema and urticaria. Systemic symptoms of diarrhea, pain and nausea	Unspecified	1-12 weeks	3/12 tolerated readministration with 1/10th original dose, 9/12 discontinued
2018	Spinelli[82]	No details	6.5 per kg	No details	Unspecified number of those with skin rashes discontinued drug and switched to chloroquine
2018	Matsuda[84]	Maculopapular erythema, pruritus	200	2 weeks	Continuation of hydroxychloroquine with topical steroid adjunct
2019	Miyagawa[91]	No details	200-400	1-4 weeks	Disappeared after discontinuation
2019	Gonzalez[99]	Lichenoid, urticarial, or exanthematous eruptions	Unspecified	1-2 weeks	Disappeared after discontinuation
2019	Takamasu[92]	Maculopapular, generalized	200-300	15-40 days	14/28 required discontinuation, 13/28 tolerated desensitization, 1/28 re-experienced eruptions

Continued

Table III. Cont'd

Year	First author	Description of skin eruption and systemic symptoms	Dosage, mg/d	Time to adverse effect	Resolution/treatment
2019	Ototake[94]	Maculopapular erythema	200-400	2-3 weeks	Disappeared after discontinuation
2019	Barailler[96]	Papular pruritic erythematous lesions with hyperpigmentation and palmar desquamation	200-400	8 weeks	Desensitization protocol
2019	Tal[97]	Hypersensitivity reactions	200-400	1-3 weeks	Desensitization protocol

Finally, the review was focused on dermatology adverse effects related to hydroxychloroquine only, and therefore, studies that pooled data regarding adverse dermatologic effects to antimalarials in general may not have been captured or may have been excluded if adverse reactions specifically related to hydroxychloroquine could not be determined.

CONCLUSION

As one of the fundamental drugs prescribed in dermatology and rheumatology, hydroxychloroquine is generally efficacious, safe, and well tolerated. However, dermatologic adverse effects—those involving the skin, hair, or nails—are both a frequent and significant complication. This systematic review elucidated and characterized the hundreds of adverse reactions associated with hydroxychloroquine. These results outlined which reactions are most common and outlined possible risk factors (ie, cumulative dose) for the development of adverse effects. Although most of these were not life-threatening reactions, any indication that a treatment may have harmful effects should be recognized.

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