Table I. Specimen information*

Category	Experimental findings	FF+, n/total (sensitivity %)
Species identification	Definitive species not identified	8/19 (42.1)
	Mycobacterium avium-intracellulare	9/13 (69.2)
	Mycobacterium tuberculosis complex	2/6 (33.3)
	Mycobacterium marinum	2/6 (33.3)
	Mycobacterium abscessus	2/3 (66.7)
	Mycobacterium fortuitum	1/2 (50.0)
	Mycobacterium haemophilum	2/2 (100.0)
	Mycobacterium kansasii	2/2 (100.0)
Culture/ molecular sensitivity	Culture	30/40 (75.0)
	Gene probe	18/19 (94.7)
	DNA sequencing	9/9 (100)
	MALDI-TOF	3/3 (100)
	HPLC	1/1 (100)
	PCR	7/17 (41.2)
Biopsy site	Cutaneous	12/21 (57.1)
	Lung	11/16 (68.8)
	Lymph node	2/9 (22.2)
	Gastrointestinal	3/6 (50.0)
	Cardiac	0/1 (0.0)

FF, Fite-Faraco; *HPLC,* high-performance liquid chromatography; *MALDI-TOF,* matrix-assisted laser desorption/ionization time of flight; *PCR,* polymerase chain reaction.
*Auramine-rhodamine was the true positive reference stain.

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Retrospective analysis of dermatologic adverse events associated with hydroxychloroquine reported to the US Food and Drug Administration

To the Editor: Hydroxychloroquine is approved by the US Food and Drug Administration (FDA) for treatment of malaria, systemic lupus erythematosus, and rheumatoid arthritis (RA).[1] Since it is commonly prescribed for both FDA-indicated and off-label uses, associated dermatologic adverse events merit careful consideration.[2] In this study, we analyzed the US FDA Adverse Event Reporting System (FAERS) for common dermatologic adverse events associated with hydroxychloroquine.[3]

From January 1, 1970, to December 31, 2019, 28,220 adverse reactions associated with hydroxychloroquine/Plaquenil (Sanofi-Synthelabo Inc, Paris, Fance) were reported to FAERS, with 11,471 categorized as skin/subcutaneous tissue/mucosal disorders. After grouping similar reaction types and excluding events with fewer than 40 cases, 9242 remained for final analysis (Table I).

The most common reactions were drug hypersensitivity reactions/rash/dermatitis (5670 cases; 61.4%). Other relatively common events were pruritus and urticaria. Nail changes, skin hyperpigmentation, mucosal, and hair disorders represented 1.9% (n = 178), 1.8% (n = 166), 1.2% (n = 112), and 0.5% (n = 47) of cases, respectively. Serious dermatologic events including Stevens-Johnson syndrome/toxic epidermal necrolysis, skin necrosis, and vasculitis represented 335 cases (3.6%) (Table I). Ages were reported for 5758 patients, with most 41 to 64 years (46.4%) or 65 to 85 years old (28.0%). Sex was reported for 8704 individuals; most were female (7287; 83.7%) (Table II).

These FAERS findings share some similarities with those in a systematic review of 689 hydrtplay @|

Table I. Most common dermatologic adverse reaction associated with hydroxychloroquine (N = 9242)

Adverse reactions	Patients, n (%)
Drug hypersensitivity/rash/rash, pruritic/drug eruption/dermatitis/ rash, maculopapular/ rash, erythematous/allergic dermatitis/erythema/toxic skin eruption/rash, macular/rash, popular/rash, vesicular	5670 (61.4)
Pruritus	526 (5.7)
Urticaria	419 (4.5)
Psoriasis/pustular psoriasis/ dermatitis psoriasiform	297 (3.2)
Skin ulcer/skin fissures/ skin erosion	243 (2.6)
Nail changes/onycholysis/ onychomadesis/nail discoloration	178 (1.9)
Skin hyperpigmentation/ pigmentation disorder/ skin discoloration	166 (1.8)
Skin exfoliation/dermatitis exfoliative/dermatitis exfoliative generalized	150 (1.6)
Stevens-Johnson syndrome/ toxic epidermal necrolysis	135 (1.5)
Panniculitis	119 (1.3)
Photosensitivity reaction	116 (1.3)
Blister	115 (1.2)
Angioedema	114 (1.2)
Skin necrosis	113 (1.2)
Oral mucosal exfoliation/ mucosal inflammation/ mucosal ulceration/oral mucosal blistering/mucosal erosion	112 (1.2)
Hyperhidrosis	111 (1.2)
Cutaneous vasculitis/vasculitis rash/hypersensitivity vasculitis	87 (0.9)
Acute generalized exanthematous pustulosis	80 (0.9)
Drug reaction with eosinophilia and systemic symptoms	79 (0.8)
Erythema multiforme	78 (0.8)
Dry skin/eczema	76 (0.8)
Pemphigus	73 (0.8)
Acne/acne cystic	71 (0.8)
Ecchymosis/purpura/skin hemorrhage	67 (0.7)
Alopecia/hair loss/hair texture abnormality/hair color changes	47 (0.5)

Table II. Demographics of patients with dermatologic adverse reaction associated with hydroxychloroquine

Characteristics	Patients, n (%)
Age (n = 5758)	
0-1 mo	28 (0.5)
2 mo to 2 y	0 (0.0)
3-11 y	47 (0.8)
12-17 y	95 (1.6)
18-40 y	1279 (22.2)
41-64 y	2669 (46.4)
65-85 y	1611 (28.0)
>85 y	29 (0.5)
Sex (n = 8704)	
Female	7287 (83.7)
Male	1417 (16.3)
Indication (n = 9141)	
Rheumatoid arthritis	7509 (82.1)
Mixed connective tissue disease	590 (6.5)
Antiphospholipid syndrome	365 (4.0)
Juvenile idiopathic arthritis	130 (1.4)
Psoriatic arthropathy	114 (1.2)
Fibromyalgia	107 (1.2)
Dermatomyositis	98 (1.1)
Adenomatous polyposis coli	78 (0.9)
Systemic lupus erythematosus	65 (0.7)
Ankylosing spondylitis	55 (0.6)
Crohn's disease	12 (1.2)
Sjögren syndrome	10 (0.1)
Chronic cutaneous lupus erythematosus	5 (0.1)
Behçet disease	3 (0.1)

Add/Remove Over/Underlayoxychloroquine-associated dermatologic events. In the review, the most common event was drug eruption (358 cases, 51.9%); pruritus (62; 8.9%) was relatively frequent.[1] A notable difference was the high incidence of skin hyperpigmentation (116; 32.4%) in the systematic review versus FAERS (166; 1.8%). Nail changes were 5 times more common in FAERS, which is likely because the systematic review included only melanonychia cases. Although age and sex distributions were similar between the 2 studies, there were significant differences in drug indications. In the systematic review, the most common indications were lupus erythematosus (72%) and RA (14%), whereas in FAERS they were RA (82.1%), mixed connective tissue disease (6.5%), and antiphospholipid syndrome (4.0%) (Table II). The large difference in indications between the 2 studies is likely due to study design and estimated US disease prevalence (RA, 1,360,000; systemic lupus erythematosus, 322,000).[4]

The most common adverse reaction in our data set was drug hypersensitivity/rash/dermatitis. Hydroxychloroquine-associated drug rashes typically ensue within 4 weeks of drug initiation and resolve after several weeks of drug discontinuation. Topical and oral steroids may

mitigate symptomatic rashes. Patients may be switched to another antimalarial; desensitization or dose titration may be attempted if hydroxychloroquine is the best/only treatment option.[5] Patients with adverse events, including pruritus (526; 4.7%) and urticaria (419; 4.5%), may also benefit from dose escalation regimens.

This study is subject to several limitations. FAERS data are self-reported by physicians, pharmaceutical companies, and patients, without corroboration. Some case information, dosing/cumulative dosing, and hydroxychloroquine prescribing by year were not available. Non-FDA indications for hydroxychloroquine (mixed connective tissue disease, antiphospholipid syndrome) were included in the data set.

This study substantiates previous studies showing that drug rashes were the most common dermatologic adverse reaction with hydroxychloroquine. We also highlight some of the less frequent and more serious adverse reactions including Stevens-Johnson syndrome/toxic epidermal necrolysis, skin necrosis, and vasculitis.[6]

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Intranasal butorphanol rescue therapy for the treatment of intractable pruritus: A case series from the Johns Hopkins Itch Clinic

To the Editor: Chronic itch that is refractory to conventional therapy is a debilitating symptom that can be difficult to manage clinically. With limited United States Food and Drug Administration-approved therapies specifically targeting itch, there is a clinical need for rapid-acting agents that can disrupt the itch-scratch cycle for patients with refractory chronic pruritus.

Although the mechanism of pruritus is poorly understood, recent breakthroughs highlight a key role for the opioid axis where μ-opioid receptor agonism is thought to potentiate itch, while κ-opioid receptor agonism may reduce itch.[1,2] A recent study saw the rapid reversal of pruritus with naloxone infusion, a μ-opioid antagonist, while other reports have demonstrated significant promise for butorphanol, a commercially available μ-opioid antagonist and κ-opioid agonist, as a salvage therapy providing rapid relief for chronic itch that is refractory to standard first-line therapies.[1,2]

Most reports to date however describe the effectiveness of butorphanol administration for morphine-induced pruritus, because analgesic opioid agents often produce itch as an adverse effect.[2,3] As such, few studies have described the clinical implementation of intranasal butorphanol in treating intractable pruritus associated with a variety of etiologies. We investigated the efficacy of intranasal butorphanol as a rescue therapy for chronic, refractory pruritus.

We report a series of 16 patients who were treated with a butorphanol, 10 mg/mL inhaler as needed, up to every 4 hours for intractable pruritus from June 2017 to July 2019 at the Johns Hopkins Itch Clinic. We conducted a retrospective medical record review and collected data regarding patient characteristics, diagnosis, dose and duration of previously tried therapies, adverse effects, compliance, comorbidities, and improvement in pruritic symptoms using patient- reported outcomes, the worst itch numerical rating scale (WI-NRS), and quality of life survey measures, which were analyzed using paired *t* tests.