RESEARCH LETTER

Cutaneous drug eruptions associated with COVID-19 therapy

To the Editor: The emergency conditions imposed by the coronavirus disease 2019 (COVID-19)[1] pandemic have forced drug regulatory agencies, from the Food and Drug Administration to the European Medicines Agency, to allow the use of drugs that are not tested and approved for this precise condition. Severe cutaneous adverse drug reactions[2] are rare, ranging from 5 cases per million of acute generalized exanthematous pustulosis and drug reaction with eosinophilia systemic symptoms to 1 case per million of toxic epidermal necrolysis. However, hundreds of lives could be affected if millions of patients are exposed. The cutaneous adverse drug reactions rate may increase as a consequence of the virus and drug interactions, as already occurs with Epstein-Barr virus, cytomegalovirus, human herpesvirus 6, and HIV. Thus, reporting cases is of paramount importance to allow pharmacovigilance agencies to estimate the effective incidence. Table I shows drugs empirically used to treat COVID-19 and several possible skin reaction patterns for rapid consultation by clinicians.

A typical example of a wide spectrum of cutaneous adverse drug reactions associated with a drug used to treat COVID-19 is hydroxychloroquine, which is associated with acute generalized exanthematous pustulosis, drug reaction with eosinophilia systemic symptoms, and lethal toxic epidermal necrolysis.[3] Antibiotics, as well as antiretrovirals, are associated with a high risk of drug eruptions,[2] whereas other experimental drugs, such as remdesivir, are poorly characterized in the literature, with unknown frequencies and risk factors for cutaneous adverse drug reactions. Tocilizumab is a potential inhibitor of multiple cytochrome enzymes, including CYp450, and increased levels of concomitant drugs or unstable metabolites may lead to skin toxicity, as well as delayed hypersensitivity reactions. Intravenous immunoglobulins are associated with cutaneous adverse events in up to 6% of patients. A recent Italian study on skin manifestations associated with COVID-19 revealed that approximately 40% of eruptions are potentially drug related.[4]

Another challenge is cutaneous adverse drug reaction management in the COVID-19 course, owing to the risk of additional adverse effects, mainly caused by drug interactions. Symptomatic treatment with antihistamines, such as mizolastine and ebastine, can prolong the QT interval and worsen the potential effects of hydroxychloroquine or azithromycin, triggering severe cardiac arrhythmia.[1] Cetirizine might be a safer drug in cases of itching maculopapular and urticaria angioedema reactions. Systemic corticosteroids are controversial for severe cutaneous adverse drug reactions, with case-control analysis[5] suggesting prolonged disease duration or progression, which are the same concerns that are currently emerging with COVID-19.[1]

The effects of the COVID-19 pandemic are without precedent, and the exponential rate of lethal disease has entailed the use of empirical drug protocols, often borrowed from those used for other diseases, in the wait for a vaccine. Occurrence of severe cutaneous adverse drug reactions is predictable, and dire consequences can be avoided if the medical community is aware of the problem. Dermatologists' expertise might be an added value to promptly recognize different cutaneous reaction patterns, support patient assessment, and provide adequate management.

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Table I. List of main drug categories and selected active principles currently used or under evaluation for COVID-19 management, with possible related cutaneous adverse reactions from the literature

Drugs	Cutaneous adverse reactions	Suggested references, by first author
Antipyretics (acetaminophen; cautious use of other nonsteroidal anti-inflammatory drugs is usually recommended)	Pruritus Rash Urticaria angioedema SJS TEN Delayed hypersensitivity reaction	Lee SY, et al. *Allergy Asthma Immunol Res*. 2019;11(2):212-221. Watanabe H, et al. *J Dermatol*. 2016; 43(3):321-324. Halevi A, et al. *Ann Pharmacother*. 2000;34(1):32-34. Ibáñez, M.D, et al. *Allergy*. 1996;51:121-123.
Hydroxychloroquine/chloroquine	Pruritus Urticaria Alopecia Hair bleaching Mucocutaneous hyperpigmentation Photosensitive eruption Sweet syndrome Psoriasis flare Exfoliative dermatitis Erythroderma AGEP GPFE SJS TEN DRESS	Sharma AN, et al. *J Am Acad Dermatol*. 2020;S0190-9622(20)30564-8. Bodard Q, et al. *Rev Med Interne*. 2020; 41:289-292. Liccioli G, et al. *Pharmacology*. 2019;104(1-2):57-59. Schwartz RA, et al. *Dermatol Ther*. 2020;33(3):e13380. Pai SB, et al. *Indian J Pharmacol*. 2017; 49(1):132-134. Murphy M, et al. *Clin Exp Dermatol*. 2001;26(5):457-458.
Lopinavir/ritonavir or darunavir/ritonavir	Pruritus Maculopapular rash Urticaria angioedema Seborrheic dermatitis Alopecia Scleroderma-like lesions Lichenoid drug eruption Lipodystrophy Nail, oral, or skin hyperpigmentation Paronychia AGEP Erythema multiforme SJS Vasculitis TEN DRESS	Ghosn J, et al. *Clin Infect Dis*. 2005; 41(9):1360-1361. Calista D. *Eur J Dermatol*. 2005;15(2):97-98. Manfredi R, et al. *AIDS*. 2006;20(18): 2399-2400. Cvetkovic RS, et al. *Drugs*. 2003;63 (8):769-802. Ortiz R, et al. *AIDS*. 2008;22(12):1389-1397. Pistone G, et al. *Case Rep Dermatol*. 2014;6(2):145-149. Introcaso CE, et al. *J Am Acad Dermatol*. 2010;63(4):549-561. Sharma A, et al. *Indian J Dermatol Venereol Leprol*. 2008;74(3):234-237.
Tocilizumab	Rash Pruritus Urticarial eruption Skin infections Ulcer Psoriasiform dermatitis Anaphylaxis Hypersensitivity reaction	Koryürek ÖM, et al. *Cutan Ocul Toxicol*. 2016;35(2):145-152. Bannwarth B, et al. *Expert Opin Drug Saf*. 2011;10(1):123-131. Matsushima Y, et al. *Case Rep Dermatol*. 2019;11(3):317-321.
Remdesevir	Rashes	Grein J, et al. *N Engl J Med*. 2020;382(24):2327-2336.

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Table I. Cont'd

Drugs	Cutaneous adverse reactions	Suggested references, by first author
Baricitinib tocilizumab	Urticaria angioedema	Praveen D, et al. *Int J Antimicrob Agents*. 2020;4:105967.
	Rash	
	Palmoplantar pustulosis	Koumaki D, et al. *Eur J Case Rep Intern Med*. 2019;7(1):001383.
	Herpes simplex/zoster	
	Psoriasiform dermatitis	Matsushima Y, et al. *Case Rep Dermatol*. 2019;11(3):317-321.
	Melanoma	
	Nonmelanoma skin cancers	
Antibiotic (azithromycin or other targeted drugs for secondary infections)	Pruritus	Shaeer MK, et al. *Pharmacy*. 2019;7(3):135
	Maculopapular exanthem	
	Urticaria angioedema	Balakirski G, et al. *Cutan Ocul Toxicol*. 2017;36(4):307-316.
	Anaphylaxis	
	Fixed drug eruption	Sriratanaviriyakul N, et al. *J Med Case Rep*. 2014;8:332.
	AGEP	
	Vasculitis	Khaldi N, et al. *J Clin Pharmacol*. 2005;12(3):e264-e268.
	SJS-TEN	
	DRESS	Williams DA. *Mil Med*. 2000; 165(8):636-637.
Antifungals (allylamine, imidazoles, or others for opportunistic infections)	Pruritus	Castellsague J, et al. *BMC Dermatol*. 2002;2:14.
	Maculopapular exanthem	
	Urticaria angioedema	Chaudhary RG, et al. *Indian Dermatol Online J*. 2019;10(2):125-130.
	AGEP	
	SJS	Beltraminelli HS, et al. *Br J Dermatol*. 2005;152(4):780-783.
	Exfoliative dermatitis	
	Subacute LE	
Systemic corticosteroid (mainly dexamethasone)	Atrophy, skin fragility	Liu D, et al. *Allerg Allergy Asthma Clin Immunol*. 2013;9(1):30.
	Purpura	
	Red stretchmarks	Kannan S, et al. *Indian J Pharmacol*. 2015;47(6):696-698.
	Hypertrichosis	
	Acneiform eruption	Watts TJ, et al. *Contact Dermatitis*. 2019;81(5):384-386.
	Systemic hypersensitivity	
		Barbaud A, et al. *Curr Pharm Des*. 2016;22(45):6825-6831.
Heparin (low weight molecular)	Maculopapular, exanthema	Phan C, et al. *Ann Dermatol Venereol*. 2014;141(1):23-29.
	Urticarial type I reaction	
	Delayed type hypersensitivity	Klos K, et al. *Contact Dermatitis*. 2011;64(1):61-62.
	AGEP	
	Skin necrosis type III Arthus reaction	Komeicki P et al. *J Am Acad Dermatol*. 2007;57(4):718-721.
		Wütschert R, et al. *Drug Saf*. 1999;20(6):25-30.
Ivermectin	Edema of face and extremities	Burham GM. *Trans R Soc Trop Med Hyg*. 1993;87:313-317.
	Papular rash	
	Bullous skin lesions	Seegobin K, et al. *Am J Emerg Med*. 2018;36(5):887-889.
	TEN	
Interferons (α; β)	Hair loss	Descamps V. *Presse Med*. 2005;34(21):1668-1672.
	Induce, reveal, or worsen some dermatoses (atopic dermatitis, psoriasis, sarcoidosis, lichen)	Li C, et al. *J Int Med Res*. 2019;47(7):3453-3457.
	Sarcoidosis, lupus	Verma P, et al. *J Chemother*. 2017;29(6):380-382.
	Polymorphic erythema	
	Vasculitis	Bush AE, et al. *J Drugs Dermatol*. 2017;16(7):714-716.
	Lichenoid drug eruption	
		Lorcy S, et al. *Ann Dermatol*. 2016;143(5):336-346.

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Drugs	Cutaneous adverse reactions	Suggested references, by first author
IVIg	Urticaria	Berk-Krauss J, et al. *Int J Womens Dermatol.* 2018;4(3):170-173.
	Maculopapular exanthem	
	Anaphylaxis	Gerstenblith MR, et al. *J Am Acad Dermatol.* 2012;66(2):312-316.
	Alopecia	
	Erythema multiforme	Cohen Aubart F, et al. *Eur J Intern Med.* 2009;20(1):70-73.
	Lichenoid dermatitis	
	Eczematous eruptions	Vecchietti G, et al. *Arch Dermatol.* 2006;142(2):213-217.
	Pompholyx	
	Purpura	
	Vasculitis	

Expected incidence of the events might range from common (1/100 and <1/10 exposed persons) for pruritus, urticaria, and maculopapular exanthem to rare (1/10,000 and <1/1000) for the majority of other reactions and to very rare for severe drug reactions (5/1 million for AGEP, SJS, and DRESS and 1/1 million for TEN).

AGEP, Acute generalized exanthematous pustulosis; *DRESS*, drug reaction with eosinophilia and systemic symptoms syndrome; *GPEF*, generalized pustular figurate erythema; *IVIg*, intravenous immunoglobulins; *SJS*, Stevens-Johnson syndrome; *TEN*, toxic epidermal necrolysis.

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