COVID-19 AND DERMATOLOGY (PART II): ADVERSE MUCOCUTANEOUS REACTIONS TO MEDICATIONS AND VACCINES USED FOR COVID-19 INFECTION

Dilek Biyik Özkaya, Gamze Erfan
Acibadem Mehmet Ali Aydinlar University Faculty of Medicine

ABSTRACT

Background/Aim*: There is no proven specific or effective treatment for COVID-19 infection; therefore, many drugs are used empirically to establish control of the infection. Viral infection creates an immunologic environment and facilitate drug sensitization. With the advent of new vaccines, the future holds promise for optimism in establishing control of the pandemic. However, even vaccines are not devoid of side effects. In part II of these review series, we aimed to review the published data on mucocutaneous reactions induced by medications used for COVID-19 infection and vaccines used for COVID-19 prophylaxis.*

Materials and methods*: Literature search was performed in the databases PubMed, Scopus, and Web of Science for the relevant studies, starting from the beginning of COVID-19 pandemic until October 2021. Research on animals, studies utilizing in vitro techniques and publications irrelevant to the study's framework were excluded.*

Results*: The mucocutaneous side effects liable to medications (antimalarials, azithromycin, lopinavir/ritonavir, remdesivir, ribavirin/interferon, oseltamivir/favipiravir, darunavir, imatinib, tocilizumab, anakinra baricitinib, and other Janus kinase inhibitors, immunoglobulin therapy, colchicine, anti-TNF-α biologics, low molecular weight heparins, camostat mesylate) and vaccines used for COVID-19 infection are reviewed herein.*

Conclusion: There is a great amount of accumulated data regarding the mucocutaneous side effects of drugs and vaccines used for COVID-19 infection. In the pandemic era, it is a major goal to diagnose drug or vaccine-related mucocutaneous eruptions and distinguish them from pathognomonic, specific, or SARS-CoV-2 virus-related cutaneous eruptions. Timely diagnosis of a mucocutaneous drug/ vaccine reaction will allow for identification of the culprit and appropriate management and protect the patient from forthcoming severe drug/ vaccine reactions. Therefore, it is essential for physicians to update their knowledge regularly on mucocutaneous side effects of COVID-19 therapeutics and vaccines.

Keywords: *COVID-19, drug reaction, cutaneous side effects, SARS-CoV-2.*

DOI: 10.19193/0393-6384_2022_2_161

Received *March 15, 2021;* ***Accepted*** *January 20, 2022*

Introduction

Despite the lack of proven efficiency, many drugs are empirically used in the setting of SARS-CoV-2 (COVID-19) infection. Owing to the infection's life-threatening potential and urgent situation, most of the medications are used before appropriate clinical testing and approval by US FDA (Food and Drug Administration) and EMA (European Medicines Agency)[1,2]. As we discussed in part I of these review series, there is an assortment of cutaneous manifestations in COVID-19 infection, which may clinically simulate drug reactions. Urticarial and maculopapular eruptions of COVID-19 infection usually appear simultaneously with the systemic manifestations, yet those of drug eruptions may take a few hours or days to develop after initiation of the offender medications[3,4]. A quandary faced by a dermatologist in a patient with a nonspecific cutaneous eruption (particularly urticarial or maculopapular rash) is whether the clinical portrait arises from SARS-CoV-2 infection, or from another

viral infection, or from an agent utilized in treatment. The possibility that a given cutaneous eruption might originate from a medication/ vaccine should always be considered and a skin biopsy should be attempted whenever feasible.

Drug categories employed in the treatment and prophylaxis of novel coronavirus disease involve antimalarials, azithromycin, lopinavir/ritonavir, remdesivir, ribavirin/interferon, oseltamivir/ favipiravir, darunavir, imatinib, tocilizumab, anakinra baricitinib and other Janus kinase inhibitors, immunoglobulin therapy, colchicine, anti-TNF-α biologics, low molecular weight heparins (LMWH), camostat mesylate and COVID-19 vaccines. Every drug/vaccine has the capability to provoke adverse cutaneous reactions and each drug/vaccine harbors a separate spectrum of adverse events on the integument[5].

In part II of these review series, we aimed to overview the mucocutaneous side effects of drugs prescribed for COVID-19 infection and COVID-19 vaccines. Systemic steroids are also used as an adjunctive therapy in COVID-19 infection. However, they were excluded from discussion herein, as their side effects are well-recognized and do not diverge significantly from what has already been known.

Pathophysiologic classification of cutaneous drug eruptions

Pathophysiology of a drug reaction entails sensitization to a medication through the development of drug-specific antibodies (e.g., IgE antibodies) or drug-specific T cells.

Drug allergies may present within a few hours, but sometimes take hours, days, or weeks to develop. Immediate type hypersensitivity reactions have onset within a few hours following drug exposure; they are IgE-related, and typically present as urticaria, angioedema, serum sickness, and anaphylaxis. Delayed type hypersensitivity reactions are usually postponed and have onset within 2 to 4 weeks after drug exposure. The prototypic cutaneous counterparts are exanthematous maculopapular rash (MPR), fixed drug reaction (FDE), erythema multiforme (EM), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS) and vasculitis[5,6].

Infections set up a convenient immunologic environment, facilitating drug sensitization. Especially in viral infections, antibiotic use is associated with adverse cutaneous effects, such as urticarial and maculopapular eruptions. The typical example is the development of ampicillin rash in patients with infectious mononucleosis.

Drugs used in COVID-19 treatment

Anyimalarials

Chloroquine is a medication used for the treatment of malaria and autoimmune rheumatologic disorders, such as rheumatoid arthritis and lupus erythematosus[7]. After accumulation within lysosomes, chloroquine becomes protonated and alters cellular pH. The ability to increase the cellular pH endows chloroquine an antiviral capability.

Hydroxychloroquine (HCQ) was initially developed for the treatment of malaria and later also used for the treatment of autoimmune diseases. HCQ has anti-inflammatory, immunomodulating, anti-infective, antithrombotic, and metabolic effects (8,9). Despite being an effective medication, HCQ has multiple adverse effects such as cardiotoxicity, prolongation of QTc, ventricular arrhythmias, and vision-threatening toxic retinopathy[10,11]. Because of these side effects, the US FDA cancelled the Emergency Use Authorization of HCQ in COVID-19 infection on June 15, 2020[12]. Cutaneous side effects of antimalarials might arise in up to 11.5% of treated patients and include urticaria, MPR, exacerbation of psoriasis, pigmentation of skin, nails and mucosa, EM, SJS, TEN, DRESS, AGEP, photosensitivity and systemic eczematous contact dermatitis. Maculopapular drug eruption due to HCQ, with a latency of 2 weeks after the start of treatment, may be mistaken for maculopapular rash of COVID-19[13,23].

Azithromycin

Azithromycin is a macrolide antibiotic that binds to the 50s subunit of the ribosome and inhibits translocation of peptides and subsequently blocks protein synthesis. It has antibacterial, antiviral, and anti-inflammatory effects[24]. Rare cutaneous side effects include urticaria, angioedema, anaphylaxis, FDE, generalized red or purple skin rashes, SJS, TEN, skin peeling, AGEP, DRESS syndrome, and leukocytoclastic vasculitis[25,26].

Lopinavir/Ritonavir

Lopinavir/ritonavir is an approved antiretroviral combination, that is used in the treatment of HIV infections. The combination has antiviral effects by inhibiting the 3-chymotrypsin-like protease

and hence recently employed in the treatment of COVID-19 infections. Cutaneous reactions are frequently encountered both in the setting of HIV and COVID-19 infection and tend to affect 5% of adults and up to 12% of children. The list of adverse cutaneous phenomena comprises MPR, SJS, TEN, DRESS, AGEP, seborrheic dermatitis, leg edema, alopecia areata, skin infections, scleroderma-like lesions, pigmentation of nail and oral mucosa, exfoliative erythroderma, lichenoid eruptions, urticaria, pruritus, xeroderma, vasculitis, redistribution of body fat and facial wasting, cysts, and ingrown toenails[17,26-30].

Remdesivir

Remdesivir is a nucleotide analogue that blocks the viral RNA polymerization. Successful outcomes in Ebola virus outbreak have paved the way for its current use in COVID-19 pandemic. Cutaneous rash may develop in up to 7.55% of patients receiving remdesivir and may necessitate drug discontinuation. Unfortunately, there is lack of data on the distribution, timing, and morphology of remdesivir-related rash, that could help its differentiation from the rash caused by COVID-19, itself. Apart from MPR, nucleotide analogues have been associated with severe cutaneous adverse drug reactions (SCARs), including life-threatening SJS and TEN[17,26,31-33].

Ribavirin/Interferon

Ribavarin is a guanine analogue antiviral drug. It shows antiviral effects against HCV through inhibition of RNA polymerase and is currently being evaluated for COVID-19 treatment. Interferon, an antiviral broad-spectrum medication, is commonly used in combination with ribavirin. Cutaneous adverse reactions are encountered in 10.3-23% of patients treated with ribavirin/interferon combination. Ribavirin has been incriminated in acneiform eruptions, pruritus, xerosis, localized scleroderma, eczematous eruptions, MPR, vasculitis, alopecia, psoriasis, and lichenoid drug eruptions. The skin reactions of interferons include injection site erythema, hair loss, lichenoid eruption, psoriasis, exanthematous drug eruptions, alopecia, exacerbation of atopic dermatitis, sarcoidosis, lupus, cutaneous vasculitic lesions[17,34-38].

Oseltamivir/Favipiravir

Oseltamivir, a neuraminidase inhibitor, is a drug that has been used to treat H1N1 virus outbreak. The antiviral triphosphate favipiravir (T-705) blocks viral replication by inhibiting RNA polymerase. Cutaneous reactions to oseltamivir are relatively rare (< 1%), although it has been implicated in the development of SJS, TEN, angioedema, and tongue swelling. Favipiravir has been linked to AGEP, pruritus, and exanthematous drug reactions[17,39-43].

Darunavir

Darunavir, a protease inhibitor used to treat HIV, is currently within the scope of COVID-19 therapy. Documented cutaneous side effects consist of MPR, thrombocytopenic purpura, vesicular eruption, allergic dermatitis, SJS and TEN. The frequency of MPR is almost 10%; others are confronted with a frequency of less than 1%. Darunavir-related MPR usually develops after a latency period of 2 weeks and resembles COVID-19 rash. It is mild to moderate in intensity and usually shows a benign self-limiting course[17,44,45].

Imatinib

Imatinib has antiviral and immunomodulatory properties. It targets BCR-ABL and other tyrosine kinases. Cutaneous side effects, challenged in more than 20% of patients receiving imatinib, embrace MPR, edema, pigmentary disorders, psoriasiform eruption, pityriasis rosea-like eruption, AGEP, SJS, urticaria, neutrophilic dermatosis, photosensitivity, porphyria, and pseudo-porphyria[17,46,47]).

Tocilizumab

Tocilizumab is a humanized monoclonal antibody against the IL-6 receptor. Among the list of reported cutaneous adverse events are cellulitis-like skin infections, necrotizing fasciitis pruritus, pustular eruption, psoriasiform dermatitis, MPR, urticaria, new-onset cutaneous sarcoidosis, vasculitis, AGEP, SJS, and DRESS syndrome. Skin infections require close follow-up, as necrotizing fasciitis and cellulitis might have a fatal outcome[17,26,48-50].

Anakinra

Anakinra is a recombinant homologue of human IL-1 receptor antagonist that blocks IL-1 receptors. A considerable increase in survival of patients with hyper inflammation (systemic cytokine release syndrome) is attained with the use of anakinra. It is a relatively safe medication. Skin-related side effects include injection-site reactions (inflammation, erythema, itching, pain), exanthematous reaction, urticaria, anaphylaxis, and skin infections[17,26,51].

Baricitinib and the other Janus kinase inhibitors (JAK-I)

Barcitinib is a specific dual JAK-1 and JAK-2 inhibitor that can prevent viral endocytosis by blocking AAK1. It is an anti-inflammatory agent, engaged in the management of systemic hyperinflammation. Cutaneous adverse events include reactivation of latent viral infections (varicella-zoster, herpes simplex, Epstein- Barr virus), palmoplantar pustulosis-like eruptions, melanoma, and non-melanoma skin cancers, urticaria, and angioedema[26,52-54].

Immunoglobulin Therapy

Convalescent plasma therapy is characterized by a collection of antiviral immunoglobulins produced in the plasma of an immune patient who has recovered from COVID-19 infection, and their transfer to a non-immune naïve patient to enhance recovery or improve survival. Intravenous immunoglobulin is a blood product, consisting of pooled polyclonal immunoglobulin G extracted from healthy donors. It has been in use for more than 30 years. Urticaria, anaphylaxis, MPR, EM, purpuric erythema, and eczema are within the spectrum of cutaneous adverse events encountered with IV immunoglobulin or plasma infusions[17,55-58].

Colchicine

Colchicine is an anti-neutrophilic medication used for hyper inflammation, since it prevents inflammasome activation and cytokine release. Adverse effects are generally secondary to intoxication. Cutaneous adverse reactions include violaceous rash, alopecia, MPR, bullous dermatitis, erythema nodosum-like reactions, and TEN-like reactions[17,59,60].

Anti-TNF-α biologics

TNF-α is a proinflammatory cytokine that plays a pivotal role in both acute and chronic inflammation. Anti-TNF agents are frequently used to treat rheumatologic disorders. As high TNF-α levels correlate with infection severity in COVID-19 infection, anti-TNF agents are currently under scrutiny in this field as well. Cutaneous side effects include infusion and injection site reactions, psoriasis and psoriasiform-like lesions, lupus-like syndromes, cutaneous vasculitis, cutaneous infections, exanthematous drug reactions, lichenoid eruptions, granulomatous reactions, cutaneous lymphoma, symmetrical drug-related intertriginous and flexural erythema (STRIFE), epithelial skin cancers or melanoma[61-63].

Low molecular weight heparins (LMWH)

Venous thromboembolism risk increases in hospitalized patients with COVID 19 infection. LMWHs are multitalented medications in COVID-19 infection; they inhibit coagulation (anti-coagulant), block inflammatory responses (anti-inflammatory) and hinder viral entry into the cells (anti-viral). Cutaneous side effects of LMWH are injection-site reactions, heparin-induced skin necrosis (erythematous plaques, hemorrhagic blisters, necrotic ulcers, petechiae), eczema, MPR, SJS, TEN, and DRESS[17,26,64].

Camostat Mesylate

Camostat mesylate is a potent serine protease inhibitor, that can block TMPRSS2 and prevent COVID-19 entry into the cells at the early stage of the infection. Urticaria, itching, and yellow skin discoloration have been reported as relevant cutaneous side effects[65,66].

Vaccines used for COVID-19 prophylaxis

Owing to the emergency of the pandemic, the development and distribution of several COVID-19 vaccinations have been immediately authorized and approved. COVID-19 vaccines are developed by various methodologies: mRNA-based vaccines (Moderna, BioNTech/Pfizer, CureVac), viral vector vaccines (adenovirus) (AstraZeneca, Sputnik V, COVID-19 Vaccine Janssen, Convidecia), inactivated whole virus (CoronaVac, Sinopharm), recombinant protein subunit (Novavax, Sanofi/GlaxoSmithKline). Cutaneous side effects of vaccines may be interrelated either to the vaccine or to the adjuvant component.

The most frequently reported cutaneous reactions from COVID-19 vaccines are local injection site reactions (erythema, swelling, tenderness, pain, induration, and pruritus) that usually occur during the succeeding 7 days of vaccination. The mRNA-based vaccines have been allied to delayed (7-10 days) local erythematous injection site reactions (COVID arm), morbilliform rash, pityriasiform rash, psoriasiform rash, eczematous rash, exfoliative dermatitis, injection site urticaria, angioedema, papular urticaria, anaphylaxis, AGEP, and vesicular rashes. Exacerbation or worsening of preexisting dermatoses (atopic dermatitis, psoriasis, lichen planus) and recall reactions have also been

documented with mRNA-based vaccines. Moderna and Pfizer-BioNTech COVID-19 mRNA vaccines have also been incriminated in rare reports of leukocytoclastic vasculitis, allergic reaction to polyethylene glycol (PEG; as an ingredient of the vaccine), urticarial vasculitis, anaphylaxis, and bullous pemphigoid. An interesting cutaneous reaction seen with mRNA vaccines is erythema and edema involving the injection sites of dermal fillers. Sputnik vaccine has been implicated in allergic and acneiform dermatitis, alopecia, petechial rash and eczema. Convidecia vaccine-related injection site reactions (pain, induration, redness,swelling, itch), oral ulceration, and oral herpes were reported. Severe acute urticaria has been described within 48 hours of CoronaVac vaccination. CoronaVac and Oxford-AstraZeneca vaccines have been reported in the setting of STRIFE. The Oxford-AstraZeneca vaccine has been linked to severe cellulitis, vaccine-induced psoriasis, rosacea, vitiligo, and Raynaud phenomenon.

Pernio-like lesions, erythromelalgia, erythema multiforme, lichen planus, varicella-zoster and herpes simplex reactivation, pityriasis rosea-like reactions, petechial rash, and purpuric rash are other cutaneous adverse effects associated with COVID-19 vaccines[67-80].

Management

A detailed personal medical history, the complete list of medications, the time scale for each medication (illustrating the temporal relationship between medication intake and the development of cutaneous reaction) and the type of cutaneous reaction should be thoroughly appraised in all cases of suspected drug eruptions in patients with COVID-19 infection. If possible, the culprit medication should be terminated. If the intensity of the cutaneous drug reaction is mild, symptomatic treatment with antihistamines, topical, and rarely systemic corticosteroids will be all that is required. In severe cutaneous drug reactions with concomitant cytokine storm, other immunomodulators and immunosuppressants might be utilized. Delayed inflammatory reactions to dermal fillers may be treated with oral lisinopril; an angiotensin-converting enzyme receptor inhibitor. If there is proof of a skin infection, antibiotics/antifungals/antivirals might be instigated. Algorithmic appropriate management of cutaneous drug eruptions in the panorama of COVID-19 infection is shown in table I. The culprit drug in immediate-type reactions (urticaria, angioedema, anaphylaxis) can be confirmed by prick test, basophil activation test (BAT), and demonstration of specific IgE against the drug. The offender medication in delayed-type cutaneous reactions (maculopapular exanthema) may be verified through patch test, prick test with late reading, lymphocyte transformation test (LTT), and Enzyme-Linked Immunosorbent Spot (ELISPOT) test. Drug provocation test (DPT) is the gold standard for the diagnosis; however, it is reserved for patients with mild to moderate immediate or delayed-type cutaneous drug reactions and contraindicated in patients with life-threatening SCARs.

Drug Allergy **Skin reaction**	**Diagnosis**	**Management**
Immediate Urticaria, Angioedema Anaphylaxis Erythematous rash	Prick Specific IgE BAT Drug challenge (not possible if previous severe reaction)	Antihistamines Topical or systemic steroids
Delayed Maculopapular rash Fixed drug reaction SJS TEN DRESS Vasculitis Lichenoid eruptions	Patch Prick (late reading) LTT Elispot Drug challenge (not possible if previous severe reaction)	Antihistamines Topical or systemic steroids

Table I: Management of drug reactions encountered in COVID-19 infection.

Conclusion

There is a great amount of accumulated data regarding the mucocutaneous side effects of empirical drugs and vaccines used for COVID-19 infection. Drug reactions are frequent within the setting of COVID-19 infection, as the immunologic scene is appropriate for drug sensitization. Furthermore, the multiplicity of the utilized medications could hamper the identification of the offender(s) in COVID-19 infection. In the pandemic era, it is a major goal to diagnose drug or vaccine-related mucocutaneous eruptions and distinguish them from pathognomonic, specific, or SARS-CoV-2 virus-related cutaneous eruptions. Timely diagnosis of a mucocutaneous drug/ vaccine reaction will pave the way for identification and termination of the culprit, and appropriate management of the reaction. Additionally, it will safeguard the patient against forthcoming severe drug/ vaccine reactions. Therefore, it is essential for physicians to update

their knowledge regularly on mucocutaneous side effects of COVID-19 therapeutics and vaccines.

References

1) Fernandez-Nieto D, Ortega-Quijano D, Segurado-Miravalles G, Pindado-Ortega C, Prieto-Barrios M et al. Comment on: Cutaneous manifestations in COVID-19: a first perspective. Safety concerns of clinical images and skin biopsies. Journal of The European Academy of Dermatology and Venereology 2020; 34 (6): e252-e254. DOI: 10.1111/jdv.16470
2) Van Damme C, Berlingin E, Saussez S, Accaputo O. Acute urticaria with pyrexia as the first manifestations of a COVID-19 infection. Journal of The European Academy of Dermatology and Venereology 2020; 34 (7): e300-e301. DOI: 10.1111/jdv.16523
3) Galván Casas C, Català A, Carretero Hernández G, Rodríguez-Jiménez P, Fernández-Nieto D et al. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. British Journal of Dermatology 2020; 183 (1): 71-77. doi: 10.1111/bjd.19163
4) Peroni A, Colato C, Schena D, Girolomoni G. Urticarial lesions: if not urticaria, what else? The differential diagnosis of urticaria: part I. Cutaneous diseases. Journal of American Academy of Dermatology 2010;62 (4):541-55. DOI: 10.1016/j.jaad.2009.11.686
5) Cho T, Uetrecht J. How reactive metabolites induce an immune response that sometimes leads to an idiosyncratic drug reaction. Chemical Research in Toxicology 2017; 30 (1): 295-314. DOI: 10.1021/acs.chemrestox.6b00357
6) Balakirski G, Merk HF. Cutaneous allergic drug reactions: update on pathophysiology, diagnostic procedures, and differential diagnosis. Cutaneous and Ocular Toxicology 2017; 36(4): 07-316. DOI: 10.1080/15569527.2017.1319379
7) Yan Y, Zou Z, Sun Y, Li X, Xu KF et al. Anti-malaria drug chloroquine is highly effective in treating avian influenza a H5N1 virus infection in an animal model. Cell Research 2013; 23 (2): 300-302. DOI: 10.1038/cr.2012.165
8) Al-Bari MA. Chloroquine analogues in drug discovery: new directions of uses, mechanisms of actions and toxic manifestations from malaria to multifarious diseases. Journal of Antimicrobial Chemotherapy 2015;70 (6):1608-1621. DOI: 10.1093/jac/dkv018
9) Pantone D, Koudriavtseva T. Current and future use of chloroquine and hydroxychloroquine in infectious, immune, neoplastic, and neurological diseases: a mini-review. Clinical Drug Investigation 2018;38 (8): 653-671. DOI: 10.1007/s40261-018-0656-y
10) Page RL 2nd, O'Bryant CL, Cheng D, Dow TJ, Ky B et al. Drugs that may cause or exacerbate heart failure: a scientific statement from the American Heart Association. Circulation. 2016;134 (6):e32-69. DOI: 10.1161/CIR.0000000000000426
11) Block JA. Hydroxychloroquine and retinal safety. The Lancet. 1998; 351 (9105): 771. DOI: 10.1016/S0140-6736(05)78925-X
12) Commissioner of the Emergency Use Authorization. FDA. 2020. Available from: https://www.fda.gov/emer- gency-preparedness-and-response/mcm-legal-regulatory-and- policy-framework/emergency-use-authorization.
13) Mittal L, Zhang L, Feng R, Werth VP. Antimalarial drug toxicities in patients with cutaneous lupus and dermatomyositis: A retrospective cohort study. Journal of American Academy of Dermatology 2018; 78 (1): 100-106.e1. DOI: 10.1016/j.jaad.2017.09.061
14) Matsuda T, Ly NTM, Kambe N, Nguyen CTH, Ueda-Hayakawa I et al. Early cutaneous eruptions after oral hydroxychloroquine in a lupus erythematosus patient: a case report and review of the published work. The Journal of Dermatology 2018; 45 (3): 344-348. DOI: 10.1111/1346-8138.14156
15) Schwartz RA, Janniger CK. Generalized pustular figurate erythema: a newly delineated severe cutaneous drug reaction linked with hydroxychloroquine. Dermatologic Therapy 2020;33 (3):e13380. DOI: 10.1111/dth.13380
16) Kutlu Ö, Metin A. A case of exacerbation of psoriasis after oseltamivir and hydroxychloroquine in a patient with COVID-19: Will cases of psoriasis increase after COVID-19 pandemic? Dermatologic Therapy 2020; 33 (4): e13383. DOI: 10.1111/dth.13383
17) Martinez-Lopez A, Cuenca-Barrales C, Montero-Vilchez T, Molina-Leyva A, Arias-Santiago S. Review of adverse cutaneous reactions of pharmacologic interventions for COVID-19: a guide for the dermatologist. Journal of American Academy of Dermatology 2020; 83 (6): 1738-1748. DOI: 10.1016/j.jaad.2020.08.006
18) Litaiem N, Hajlaoui K, Karray M, Slouma M, Zeglaoui F. Acute generalized exanthematous pustulosis after COVID-19 treatment with hydroxychloroquine. Dermatologic Therapy 2020;33 (4): e13565. DOI: 10.1111/dth.13565
19) Dealer J, Deniau B, Battistella M, de Masson A, Bensaid B et al. Acute generalized exanthematous pustulosis induced by hydroxychloroquine prescribed for COVID-19. The Journal of Allergy and Clinical Immunology: In Practice 2020; 8 (8): 2777-2779.e1. DOI: 10.1016/j.jaip.2020.05.046
20) Abadías-Granado I, Palma-Ruiz AM, Cerro PA, Morales-Callaghan AM, Gómez-Mateo MC et al. Generalized pustular figurate erythema first report in two COVID-19 patients on hydroxychloroquine. Journal of The European Academy of Dermatology and Venereology 2021; 35 (1): 5-e7. DOI: 10.1111/jdv.16903
21) Castro Jiménez A, Navarrete Navarrete N, Gratacós Gómez AR, Florido López F, García Rodríguez R et al. First case of DRESS syndrome caused by hydroxychloroquine with a positive patch test. Contact Dermatitis 2021 ;84 (1): 50-51. doi: 10.1111/cod.13657
22) Davoodi L, Jafarpour H, Kazeminejad A, Soleymani E, Akbari Z et al. Hydroxychloroquine-induced Stevens-Johnson syndrome in COVID-19: a rare case report. Oxford Medical Case Reports 2020; 2020 (6): omaa042. DOI: 10.1093/omcr/omaa042
23) Behrangi, E, Hallaji Z, Ghiasi M, Abedini R, Ghanadan A et al. Hydroxychloroquine-induced unusual generalized

pustular cutaneous reaction as a new clinical entity: a case series. Immunoregulation 2020;3 (1): 67-72. DOI: 10.32598/Immunoregulation.3.1.8

24) Ohe M, Shida H, Jodo S, Kusunoki Y, Seki M et al. Macrolide treatment for COVID-19: Will this be the way forward? BioScience Trends. 2020; 14 (2): 159-160. DOI: 10.5582/bst.2020.03058

25) Gautret P, Lagier JC, Honoré S, Hoang VT, Colson P et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial revisited. International Journal of Antimicrobial Agents 2021; 57 (1): 106243. DOI: 10.1016/j.ijantimicag.2020.106243

26) Dordal Culla MT, Herrera-Lasso Regás V, Martí-Garrido J, Rodríguez Cumplido D, Vázquez-Revuelta P et al. Treating COVID-19: review of drug hypersensitivity reactions. Journal of Investigational Allergology and Clinical Immunology 2020; 30 (6): 385-399. doi: 10.18176/jiaci.0588

27) Cao B, Wang Y, Wen D, Liu W, Wang J et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. The New England Journal of Medicine 2020; 382 (19): 1787-1799. DOI: 10.1056/NEJMoa2001282

28) Calista D. Maculo-papular rash induced by lopinavir/ritonavir. European Journal of Dermatology 2005; 15 (2): 97-98.

29) Eyer-Silva WA, Neves-Motta R, Pinto JF, Morais-De-Sá CA. Inflammatory oedema associated with lopinavir-including HAART regimens in advanced HIV-1 infection : report of 3 cases. AIDS 2002; 16 (4): 673-674. DOI: 10.1097/00002030-200203080-00023

30) Chrysos G, Mikros S, Kokkoris S, Pastelli A, Kontochristopoulos G. Alopecia induced by lopinavir plus ritonavir therapy in an HIV patient. Journal of Drugs in Dermatology 2007; 6 (7): 742-743

31) Grein J, Ohmagari N, Shin D, Diaz G, Asperges E et al. Compassionate use of remdesivir for patients with severe Covid-19. The New England Journal of Medicine 2020; 382 (24): 2327-2336. DOI: 10.1056/NEJMoa2007016

32) Wang Y, Zhang D, Du G, Du R, Zhao J et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. The Lancet. 2020; 395 (10236): 1569-1578. DOI: 10.1016/S0140-6736(20)31022-9

33) Introcaso CE, Hines JM, Kovarik CL. Cutaneous toxicities of antiretroviral therapy for HIV: part I. Lipodystrophy syndrome, nucleoside reverse transcriptase inhibitors, and protease inhibitors. Journal of American Academy of Dermatology 2010; 63 (4): 549-61. DOI: 10.1016/j.jaad.2010.01.061

34) Arabi YM, Shalhoub S, Mandurah Y, Al-Hameed F, Al-Omari A et al. Ribavirin and interferon therapy for critically ill patients with Middle East respiratory syndrome: a multicenter observational study. Clinical Infectious Disease 2020; 70 (9): 1837-1844. DOI: 10.1093/cid/ciz544

35) Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. PLOS Medicine 2006;3 (9):e343. DOI: 10.1371/journal.pmed.0030343

36) Morra ME, Van Thanh L, Kamel MG, Ghazy AA, Altibi AMA et al. Clinical outcomes of current medical approaches for Middle East respiratory syndrome: a systematic review and meta-analysis. Reviews in Medical Virology 2018; 28 (3): e1977. DOI: 10.1002/rmv.1977

37) Kerl K, Negro F, Lübbe J. Cutaneous side-effects of treatment of chronic hepatitis C by interferon alfa and ribavirin. British Journal of Dermatology 2003; 149 (3) :656. DOI: 10.1046/j.1365-2133.2003.05481.x

38) Mistry N, Shapero J, Crawford RI. A review of adverse cutaneous drug reactions resulting from the use of interferon and ribavirin. Canadian Journal of Gastroenterology 2009; 23 (10): 677-683. DOI: 10.1155/2009/651952

39) Zuo W, Wen LP, Li J, Mei D, Fu Q et al. Oseltamivir induced Stevens-Johnson syndrome/toxic epidermal necrolysis-case report. Medicine (Baltimore). 2019; 98 (19): e15553. DOI: 10.1097/MD.0000000000015553

40) Kalsi T, Stevenson J, Wade P, Kinirons M. Tongue swelling in association with oseltamivir (Tamiflu). BMJ Case Reports 2011; 2011:bcr0620114396. DOI: 10.1136/bcr.06.2011.4396

41) Costanzo M, De Giglio MAR, Roviello GN. SARS-CoV-2: recent reports on antiviral therapies based on lopinavir/ritonavir, darunavir/umifenovir, hydroxychloroquine, remdesivir, favipiravir and other drugs for the treatment of the new coronavirus. Current Medicinal Chemistry 2020; 27 (27): 4536-4541. DOI: 10.2174/0929867327666200416131117

42) Chen C, Zhang Y, Huang J, Yin P, Cheng Z et el. Favipiravir versus arbidol for clinical recovery rate in moderate and severe adult COVID-19 patients: a prospective, multicenter, open-label, randomized controlled clinical trial. Frontiers in Pharmacology 2021; 12: 683296. DOI: 10.3389/fphar.2021.683296

43) Atak MF, Farabi B, Akbayrak A, Kalelioğlu MB, Rao BK. Acute generalized exanthematous pustulosis following treatment with favipiravir in a patient with COVID-19 without hydroxychloroquine use: report of the first case. Journal of Cosmetic Dermatology 2021; 20 (8):2387-2389. DOI: 10.1111/jocd.14304

44) Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug Discoveries and Therapeutics 2020; 14(1): 58-60. DOI: 10.5582/ddt.2020.01012

45) Lin KY, Cheng CY, Yang CJ, Tsai MS, Hsieh SM et al. Skin rash related to once-daily boosted darunavir-containing antiretroviral therapy in HIV-infected Taiwanese: incidence and associated factor. Journal of Infection and Chemotherapy 2014; 20 (8): 465-470. DOI: 10.1016/j.jiac.2014.04.006

46) Morales-Ortega A, Bernal-Bello D, Llarena-Barroso C, Frutos-Pérez B, Duarte-Millán MÁ et al. Imatinib for COVID-19: A case report. Clinical Immunology 2020; 218: 108518. doi: 10.1016/j.clim.2020.108518

47) Pretel-Irazabal M, Tuneu-Valls A, Ormaechea-Pérez N. Adverse skin effects of imatinib, a tyrosine kinase inhibitor. Actas Dermo-Sifiliograficas 2014;105 (7):655-662. doi: 10.1016/j.ad.2013.01.009

48) Matsushima Y, Hayashi A, Mizutani K, Kondo M, Nakai Y et al. Psoriasiform dermatitis developing during treatment of juvenile idiopathic arthritis with tocilizumab. Case Reports in Dermatology 2019; 11 (3): 317-321. DOI: 10.1159/000504429

49) Del Giorno R, Iodice A, Mangas C, Gabutti L. New-onset cutaneous sarcoidosis under tocilizumab treatment for giant cell arteritis: a quasi-paradoxical adverse drug reaction. Case report and literature

review. Therapeutic Advances in Musculoskeletal Disease 2019; 11: 1759720X19841796. DOI: 10.1177/1759720X19841796

50) Rosa-Gonçalves D, Bernardes M, Costa L. Necrotizing fasciitis in a patient receiving tocilizumab for rheumatoid arthritis - case report. Reumatologica Clinica (English Edition) 2018;14 (3):168-170. DOI: 10.1016/j.reuma.2016.10.008

51) Shakoor B, Carcillo JA, Chatham WW, Amdur RL, Zhao H et al. Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of macrophage activation syndrome: reanalysis of a prior phase III trial. Critical Care Medicine 2016; 44 (2): 275-81. DOI: 10.1097/CCM.0000000000001402

52) Richardson P, Griffin I, Tucker C, Smith D, Oechsle O et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. The Lancet. 2020;395 (10223): e30-e31. DOI: 10.1016/S0140-6736(20)30304-4

53) Praveen D, Puvvada RC, M VA. Janus kinase inhibitor baricitinib is not an ideal option for management of COVID-19. International Journal of Antimicrobial Agents 2020;55 (5): 105967. DOI: 10.1016/j.ijantimicag.2020.105967

54) Koumaki D, Koumaki V, Lagoudaki E, Bertsias G. Palmoplantar pustulosis-like eruption induced by baricitinib for treatment of rheumatoid arthritis. European Journal of Case Reports in Intern Medicine 2019; 7 (1): 001383. DOI: 10.12890/2019_001383

55) Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID-19. The Lancet Infectious Disease 2020; 20 (4): 398-400. DOI: 10.1016/S1473-3099(20)30141-9

56) Miyamoto J, Böckle BC, Zillikens D, Schmidt E, Schmuth M. Eczematous reaction to intravenous immunoglobulin: an alternative cause of eczema. The Journal of American Medical Association Dermatology 2014;150 (10): 1120-1122. DOI: 10.1001/jamadermatol.2014.109

57) Cao W, Liu X, Bai T, Fan H, Hong K, Song H, Han Y, Lin L, Ruan L, Li T. High-dose intravenous immunoglobulin as a therapeutic option for deteriorating patients with coronavirus disease 2019. Open Forum Infectious Diseases 2020; 7 (3): ofaa102. DOI: 10.1093/ofid/ofaa102

58) Jawhara S. Could intravenous immunoglobulin collected from recovered coronavirus patients protect against COVID-19 and strengthen the immune system of new patients? International Journal of Molecular Sciences 2020; 21 (7): 2272. DOI: 10.3390/ijms21072272

59) Stewart S, Yang KCK, Atkins K, Dalbeth N, Robinson PC. Adverse events during oral colchicine use: a systematic review and meta-analysis of randomised controlled trials. Arthritis Research and Therapy 2020; 22 (1): 28. DOI: 10.1186/s13075-020-2120-7

60) Felsenstein S, Herbert JA, McNamara PS, Hedrich CM. COVID-19: Immunology and treatment options. Clinical Immunology 2020; 215: 108448. DOI: 10.1016/j.clim.2020.108448

61) Stebbing J, Phelan A, Griffin I, Tucker C, Oechsle O et al. COVID-19: combining antiviral and anti-inflammatory treatments. The Lancet Infectious Disease 2020; 20 (4): 400-402. DOI: 10.1016/S1473-3099(20)30132-8

62) Ferro F, Elefante E, Baldini C, Bartoloni E, Puxeddu I et al. COVID-19: the new challenge for rheumatologists. Clinical and Experimental Rheumatology 2020; 38 (2): 175-180.

63) Sehgal R, Stratman EJ, Cutlan JE. Biologic Agent-Associated Cutaneous Adverse Events: A Single-Center Experience. Journal of Clinical Medicine Research 2018;16 (1-2):41-46. DOI: 10.3121/cmr.2017.1364

64) Liu J, Li J, Arnold K, Pawlinski R, Key NS. Using heparin molecules to manage COVID-2019. Research and Practice in Thrombosis and Haemostasis 2020;4 (4):518-523. DOI: 10.1002/rth2.12353

65) Breining P, Frølund AL, Højen JF, Gunst JD, Starke NB et al. Camostat mesylate against SARS-CoV-2 and COVID-19-rationale, dosing and safety. Basic and Clinical Pharmacology and Toxicology 2021; 128 (2): 204-212. DOI: 10.1111/bcpt.13533

66) Uno Y. Camostat mesilate therapy for COVID-19. Internal and Emergency Medicine 2020; 15 (8): 1577-1578. DOI: 10.1007/s11739-020-02345-9

67) Sun Q, Fathy R, McMahon DE, Freeman EE. COVID-19 vaccines and the skin: the landscape of cutaneous vaccine reactions worldwide. Dermatologic Clinics 2021; 39 (4): 653-673. DOI: 10.1016/j.det.2021.05.016

68) Robinson LB, Fu X, Hashimoto D, Wickner P, Shenoy ES et al. Incidence of cutaneous reactions after messenger RNA COVID-19 vaccines. The Journal of American Medical Association Dermatology 2021; 1 57 (8): 1000-1002

69) Blumenthal KG, Freeman EE, Saff RR, Robinson LB, Wolfson AR et al. Delayed large local reactions to mRNA-1273 vaccine against SARS-CoV-2. The New England Journal of Medicine 2021; 384 (13): 1273-1277. DOI: 10.1056/NEJMc2102131

70) McMahon DE, Amerson E, Rosenbach M, Lipoff JB, Moustafa D et al. Cutaneous reactions reported after Moderna and Pfizer COVID-19 vaccination: a registry-based study of 414 cases. Journal of American Academy of Dermatology 2021; 85 (1): 46-55. DOI: 10.1016/j.jaad.2021.03.092

71) Shimabukuro T, Nair N. Allergic reactions including anaphylaxis after receipt of the first dose of Pfizer-BioNTech COVID-19 vaccine. The Journal of American Medical Association 2021; 325 (8): 780-781. DOI: 10.1001/jama.2021.0600

72) Zhu FC, Li YH, Guan XH, Hou LH, Wang WJ et al. Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial. The Lancet 2020; 395 (10240): 1845-1854. DOI: 10.1016/S0140-6736(20)31208-3

73) Cabanillas B, Akdis CA, Novak N. Allergic reactions to the first COVID-19 vaccine: a potential role of polyethylene glycol? Allergy 2021; 76 (6): 1617-1618. DOI: 10.1111/all.14711

74) Ricardo JW, Lipner SR. Case of de novo nail psoriasis triggered by the second dose of Pfizer-BioNTech BNT162b2 COVID-19 messenger RNA vaccine. JAAD Case Reports 2021; 17: 18-20. DOI: 10.1016/j.jdcr.2021.09.009

75) Larson V, Seidenberg R, Caplan A, Brinster NK, Meehan SA et al. Clinical and histopathological spectrum of delayed adverse cutaneous reactions following COVID-19 vaccination. Journal of Cutaneous Pathology 2021:10.1111/cup.14104. (Online ahead of print) DOI: 10.1111/cup.14104

76) Stingeni L, Bianchi L, Zalaudek I, Pigatto PD, Peris K et al. Adverse cutaneous and mucous reactions from anti SARS-CoV-2 vaccines: recommendations from the Italian Society of Dermatology (SIDeMaST). Italian Journal of Dermatology and Venerology 2021; 1 56 (2): 115-117. DOI: 10.23736/S2784-8671.21.06992-3

77) Niebel D, Novak N, Wilhelmi J, Zion J, Wilsmann-Theis D et al. Cutaneous adverse reactions to COVID-19 vaccines: insights from an immuno-dermatological perspective. Vaccines (Basel). 2021; 9 (9): 944. DOI: 10.3390/vaccines9090944

78) Lim PN, Wylie G. Symmetrical drug-related intertriginous and flexural exanthema like eruption associated with COVID-19 vaccination. Clinical and Experimental Dermatology 2021: 10.1111/ced.14898. (Online ahead of print) DOI: 10.1111/ced.14898

79) Orange OM, Balta I, Yigit D, Eksioglu M. Systemic drug-related intertriginous and flexural exanthema like eruption after CoronaVac vaccine. Journal of The European Academy of Dermatology and Venereology 2021; 35 (10): e634-e635. DOI: 10.1111/jdv.17454

80) Agaronov A, Makdesi C, Hall CS. Acute generalized exanthematous pustulosis induced by Moderna COVID-19 messenger RNA vaccine. JAAD Case Reports 2021; 16: 96-97. DOI: 10.1016/j.jdcr.2021.08.013

Dilek Biyik Özkaya, (orcid no:000-0002-5003-5346)
Gamze Erfan, (orcid no: 0000-0003-0000-5568)

Acknowledgement: The authors extend their gratitude and appreciation to Prof. Emel Öztürk Durmaz, M.D., whose comments and criticism ensure the quality of this review.

Corresponding Author:
Dilek Biyik Özkaya, MD
Atakent Acibadem Hospital, Halkali Merkez
Turgut Özal Bulvari No:16, 34303 Küçükçekmece/Istanbul
Email: dilekozkaya@gmail.com
(Turkey)