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Emerging treatments in COVID-19: Adverse drug reactions including drug hypersensitivities

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There is a desperate need to identify effective treatments for coronavirus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] Most drugs currently explored in this pandemic are repurposed antiviral and immunomodulatory drugs. Adverse drug reactions (ADRs), when encountered, add an additional level of complexity to the management of patients with COVID-19. Given these are repurposed drugs, there is already an experience base in dealing with their ADRs. In this review, we aim to offer guidance from an allergy and pharmacology perspective on ADRs, including drug hypersensitivity reactions (DHRs), caused by drugs currently used for the treatment of COVID-19.

DRUGS EXPLORED FOR THE TREATMENT OF COVID-19

The clinical spectrum of a SARS-CoV-2 infection can range from mild flu-like symptoms to acute respiratory distress syndrome and multiple organ dysfunction compounded by an excessive proinflammatory host response ("cytokine storm").

Drugs repurposed for the treatment of COVID-19 are aimed at either modulating virus-host interaction or disrupting the viral life cycle.[1]

Drugs designed to block receptor-mediated endocytosis and thereby viral cell entry include the influenza drug umifenovir. The antimalarial drugs chloroquine and hydroxychloroquine were initially considered to provide additional therapeutic benefit due to their immunomodulatory properties, but given the lack of efficacy and concerns about safety, the US Food and Drug Administration withdrew them from use in COVID-19 in June 2020. Promising drugs that block virus synthesis by interfering with RNA-dependent RNA polymerase are nucleoside analogues such as remdesivir and favipiravir. Agents that disrupt the viral life cycle by stalling the release of new virus particles from infected cells include protease inhibitors such as lopinavir and ritonavir. Host-targeted treatments for COVID-19 intended to modify the detrimental effects of various proinflammatory cytokines include TNF-α inhibitors such as infliximab, IL-6 and IL-6 receptor inhibitors such as tocilizumab and sarilumab, IL-1 inhibitors such as anakinra and canakinumab, IFN-γ inhibitors such as emapalumab, and Janus kinase inihibitors such as ruxolitinib, tofacitinib, baricitinib, and upadacitinib.[1]

ADRs IN COVID-19

ADRs are classified into type A, dose-dependent reproducible side effects and type B, immunologically or nonimmunologically triggered DHRs/drug allergy reactions. Most DHRs are categorized by the suspected underlying pathomechanism into either immediate-type (IgE- or non–IgE-mediated) or delayed-type (T-cell–mediated or p-i concept [pharmacologic interaction with immune receptors]) reactions.[2] ADRs to biologicals have to be distinguished from infusion reactions and are classified into 4 hypersensitivity reaction patterns, namely, type I–like, cytokine release, mixed (type I/cytokine release), and type IV reactions, and are described for all biologicals used in COVID-19.

Any organ system, but also multiple organs simultaneously, can be affected by ADRs from drugs used in COVID-19 (Fig 1). In multiple organ dysfunction associated with COVID-19, ADR are an important differential diagnosis.

Cutaneous manifestations are common with DHRs and are therefore considered in detail in Fig 2.[3] Immediate-type DHRs appear within minutes after drug intake, and the viral entry inhibitor umifenovir as well as the biologicals are common culprits with symptoms such as urticaria, angioedema, and anaphylaxis. Delayed-type DHRs present in various clinical manifestations,

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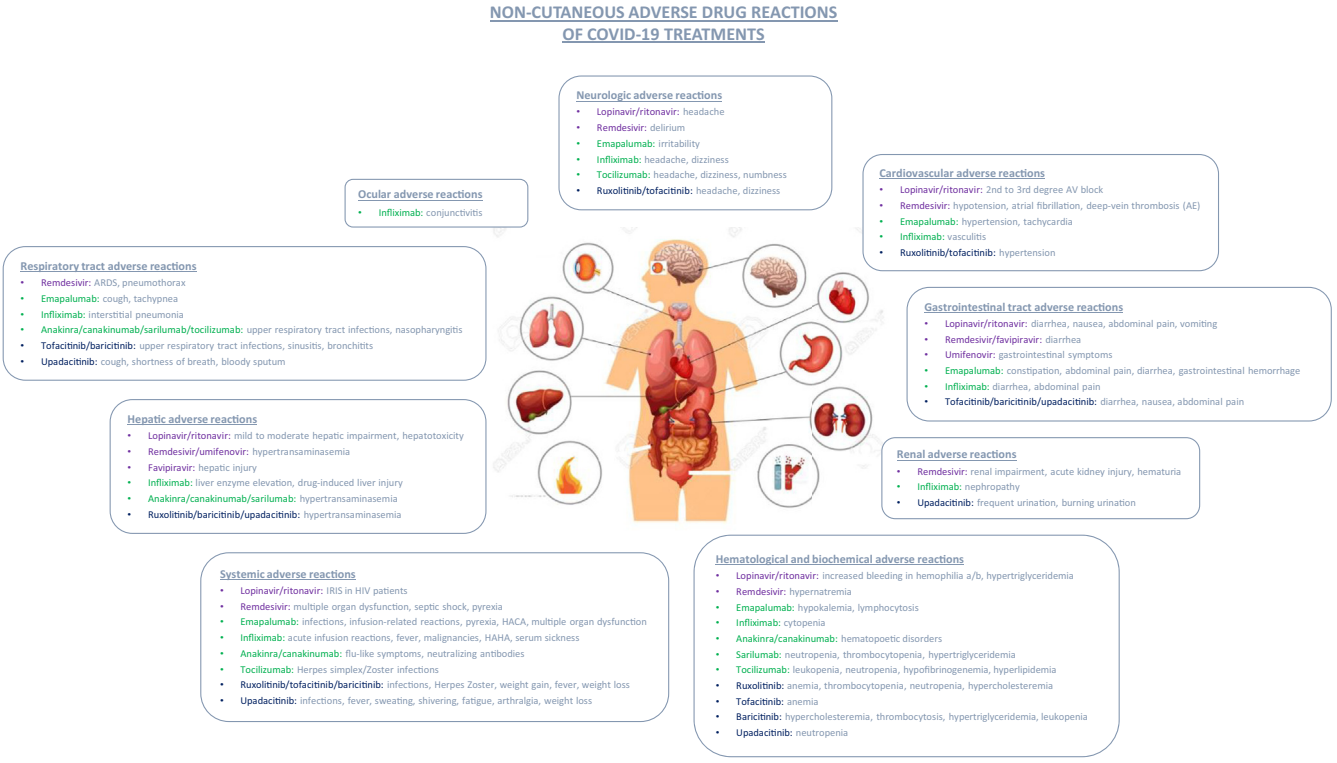

FIG 1. Noncutaneous ADRs to drugs used in COVID-19, sorted by organ system. *AE,* Adverse event; *ARDS,* acute respiratory distress syndrome; *AV,* atrioventricular; *HACA,* human antichimeric antibody*; HAHA,* human antihuman antibody; *IRIS,* immune reconstitution inflammatory syndrome. Color distribution: *violet* antiviral drugs, *green* inflammatory cytokine inhibitors, *dark blue* Janus kinase inhibitors.

and are differentiated primarily by their morphology and organ involvement (Fig 2).

Parainfectious exanthems are an important differential diagnosis of DHRs. Some viruses, mainly of the herpes group, Coxsackie A or ECHO viruses, commonly elicit parainfectious exanthems, whereas coronaviruses, in particular SARS-CoV-2, do not seem to do so as frequently. In general indicative, but not conclusive, for a viral trigger of exanthems are distal lesions with a proximal spread toward the trunk.

A Spanish publication has categorized cutaneous manifestations of COVID-19 into 5 clinical patterns: acral areas of erythema with vesicles or pustules (pseudo-chilblain), other vesicular eruptions, urticarial lesions, maculopapular lesions, and livedo or necrosis.[4] An association with "receiving drugs" was more frequent in those with maculopapular, livedoid, and urticarial lesions, compared with those with pseudo-chilblain or vesicular lesions.[4] Recalcati reported uncomplicated cutaneous manifestations in approximately 20% of 88 patients, mainly erythematous rash, urticaria, and chickenpox-like vesicles.[5] Hedou et al responded with a prospective study on skin manifestations of SARS-CoV-2–positive patients, identifying 1 case of urticaria in the prodromal phase, 2 erythematous rashes and 1 case of urticaria as well as 1 reactivation of oral herpes simplex during the infection in a total of 103 patients.[6] Furthermore, polymorphic rash and erythema of the palms and soles appear to be typical for the newly described Kawasaki-like disease in COVID-19–affected children, which is currently suspected to develop as a consequence of SARS-CoV-2–induced cytokine storm/macrophage activation syndrome.[7]

The evolving knowledge of frequent COVID-19–induced coagulopathies and thrombophilic and hyperviscous states may help to understand the occurrence of petechiae, chilblain-like lesions and livedo reticularis as a consequence of cytokine-induced inflammation and microthrombus formation facilitated by viral binding to angiotensin-converting enzyme 2.[8]

In the ongoing COVID-19 pandemic, classical presentations of ADRs are increasingly reported: acute generalized exanthematous pustulosis mainly to chloroquine/hydroxychloroquine (before they were withdrawn as recommended medications for COVID-19), recently also to cefditoren; symmetrical drug-related intertriginous and flexural exanthema in a COVID-19–positive patient without a clearly identifiable elicitor; and 1 case of potential Stevens-Johnson syndrome/toxic epidermal necrosis overlap with an unclear elicitor (potentially virus-induced).[9,10] There are no reports of drug reaction with eosinophilia and systemic symptoms or fixed drug eruption in the COVID-19 context so far.

MANAGEMENT OF DRUG HYPERSENSITIVITY IN COVID-19

An initial assessment of the chronology of drug exposure and symptom onset is required to identify the suspected offending agents. Notably, treatment durations of the repurposed drugs for COVID-19 are considerably shorter compared with the usual indication in chronic diseases.

Sometimes, switching within a drug group is possible (eg, switching from anakinra to canakinumab). Otherwise, avoidance of the most likely culprit drug would be recommended.

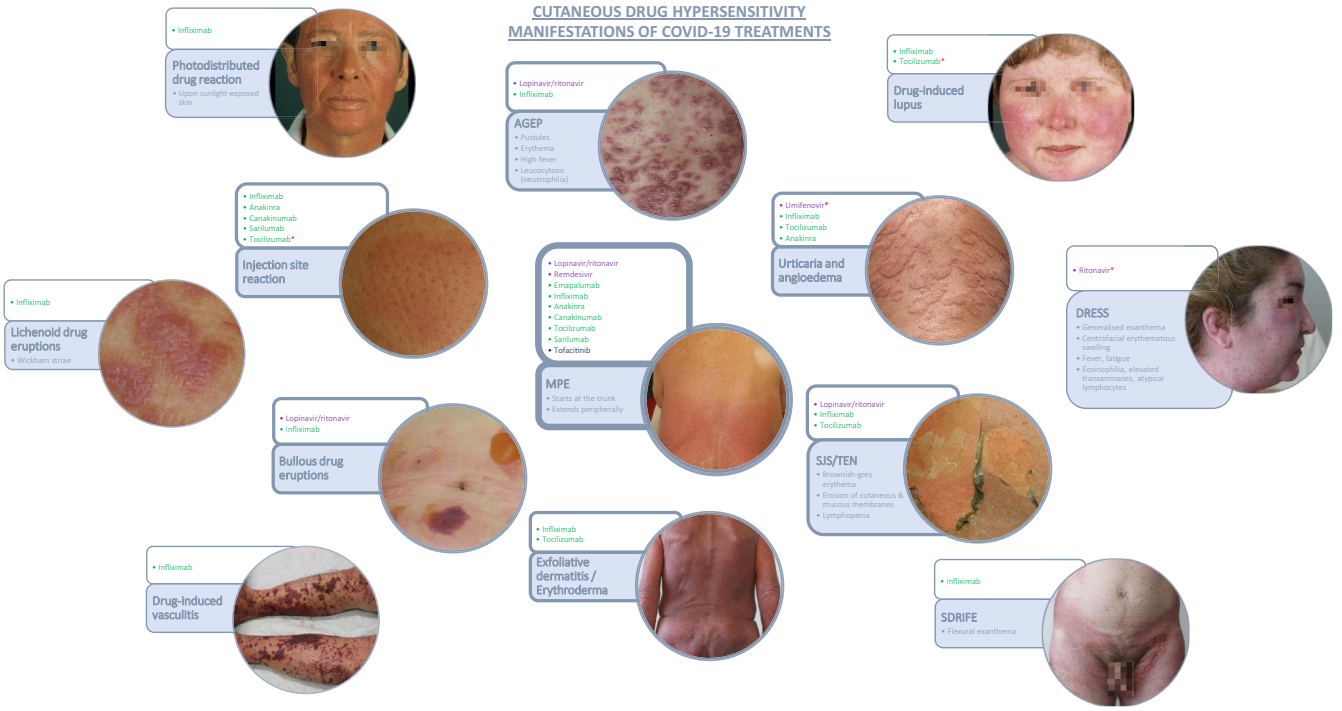

FIG 2. Cutaneous drug hypersensitivity manifestations of drugs used in COVID-19. *AGEP*, Acute generalized exanthematous pustulosis; *DRESS*, drug reaction with eosinophilia and systemic symptoms; *FDE*, fixed drug eruption; *MPE*, maculopapular exanthema; *SDRIFE*, symmetrical drug-related intertriginous and flexural exanthema; *SJS/TEN*, Stevens-Johnson syndrome/toxic epidermal necrolysis; *UMC*, Uppsala Monitoring Centre; *WHO*, World Health Organization. Color distribution: *violet* antiviral drugs, *green* inflammatory cytokine inhibitors, *dark blue* Janus kinase inhibitors. Line width of frames relates to the frequency of occurrence of the respective hypersensitivity manifestations. *WHO Collaborating Centre for International Drug Monitoring (UMC) signal in VigiLyze.[3] Caveat statement: Data from spontaneous ADR reporting are inhomogeneous as a result of different reporting policies worldwide and are vulnerable to underreporting and reporting bias. The information is therefore not homogeneous, at least with respect to origin and likelihood that the pharmaceutical product caused the adverse reaction. The conclusions drawn on the basis of these data do not necessarily represent the opinion of the UMC or the WHO.

Irrespective of the offending drug, treatment of suspected DHRs should be symptom-guided (eg, antihistamines for pruritus), and in anaphylaxis according to guidelines. In general, drug exanthems are treated with topical and, if necessary, systemic corticosteroids, but other immunomodulators and immunosuppressants might play a role in patients with COVID-19 with severe cutaneous adverse reactions and concurrent cytokine storm. Occasionally, a further increase in symptoms occurs over subsequent days despite discontinuation of the triggering agent, which may suggest an additional DHR to a substitute medication, an overhang of the initial ADR momentum, or, in the case of patients with COVID-19, a cytokine storm.

For certain phenotypes of DHRs, drug desensitization is a theoretical option if the culprit drug is clearly needed and adequate therapeutic alternatives are not available. Drug desensitization is not an option, however, for infusion reactions in patients with COVID-19. Although desensitization in specialized centers has been shown to be safe in cancer and chronic disease, in the context of highly inflammatory processes such as COVID-19, there are considerable risks for breakthrough reactions, and there are no published cases of attempts to desensitize in patients with COVID-19.

A specialist allergy assessment is mandatory between 6 weeks and 6 months later, with the aim to confirm the suspected DHR or consequently delabel the patient. This avoids misleading results from an overhanging nonspecific immune activation, causing false positives, and optimizes diagnostic yield, avoiding false negatives. For immediate-type DHRs, testing should include skin tests and, if available, serological testing. *In vitro* functional assays such as basophil activation tests can be considered. In delayed-type DHRs, the main diagnostic measures are intradermal tests with late reading after 48 hours or patch testing. *In vitro* lymphocyte transformation test can be of added value.

CONCLUSIONS

COVID-19 is a complex immunologic interplay between the virus and the host. ADRs to COVID-19 treatments can pose an additional challenge and need to be distinguished from the inflammatory COVID-19 clinical picture. Several agents being given together make attribution to a single agent challenging. Immediate management following ADRs is avoidance of that drug, identification of a suitable alternative, and symptom-guided treatment of the ADR. For DHRs, detailed documentation aids in subsequent allergological workup. Further studies are needed to help differentiate clinical symptoms attributable to COVID-19 from symptoms associated with ADRs. As the amount of data available from randomized

controlled trials and pharmacovigilance studies will increase over the coming months, the picture of ADRs in the COVID-19 context will become clearer.

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