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Drug repurposing of dermatologic medications to treat coronavirus disease 2019: Science or fiction?

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Abstract No pharmaceutical products have been demonstrated to be safe and effective to specifically treat coronavirus disease 2019 (COVID-19); therefore, the therapy administered to infected patients remains symptomatic and empiric. Alongside the development of new, often high-cost drugs, a different tactic is being applied in parallel, investigating long-established, inexpensive medications originally designed for a variety of diseases to study their potential in treating COVID-19.

The skin is the largest organ of the human body. With more than 3,000 skin conditions identified, the specialty of dermatology offers a rich armamentarium of systemic therapeutic agents aimed to treat the various chronic immunologically mediated, metabolic, infectious, occupational, inherited, or paraneoplastic dermatoses. Dermatologists have extensive experience with many drugs that have demonstrated promising in vitro antiviral action (directly targeting the viral replication). Many of these drugs have been used as nonspecific immunosuppressive strategies, such as glucocorticoids, synthetic antimalarials, colchicine, or other immunomodulators, and a number of targeted therapeutics have been directed at controlling hyperinflammatory processes similar to the “cytokine storm” associated with COVID-19 infection. We discuss several dermatologic drugs that have already been used or may have a promising role in the treatment of COVID-19.

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“In these matters, the only certainty is that nothing is certain.”

Pliny the Elder (23/24 – 79 CE), *Naturalis Historia, Vol. VI*

**Introduction**

Since the emergence of the coronavirus disease 2019 (COVID-19) in December 2019 in Wuhan, China, and its dramatic acceleration to pandemic status,¹ researchers around the world have joined the effort to develop vaccines for the prevention of and new drugs for the treatment of the disease. The vaccines are here, several of them approved, and offer approximately 6 to 12 months of protection. As promising as these vaccines are, however, there is still a long way to go.

Despite the huge amount of work in this field in the past year, according to the World Health Organization (WHO), there is currently no effective and safe medication for prevention or treatment of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection that caused the current global health crisis.²

Despite pressure from the constantly rising number of affected people, the US Food and Drug Administration (FDA) and the European Medicines Agency have not approved any agents for treating COVID-19³; no pharmaceutical agents, moreover, have been shown to be safe and effective for the treatment of COVID-19.

At present, the therapy administered to COVID-19 patients remains symptomatic and empiric; whereas the seriously ill patients are provided with organ support.³ A number of medications have been suggested as potential investigational therapies, many of which are now being or will soon be studied in clinical trials.⁴

Alongside the development of new, often high-cost drugs, a different tactic is being applied in tandem—investigating well-established, inexpensive medications originally designed for a variety of diseases—to determine whether they could be used to treat COVID-19. It is ethically acceptable to offer to the most severely affected patients an “off-label” treatment with existing drugs that have been proven to be both effective and safe for humans and can be repurposed to treat this novel disease.

Repurposing of well-established drugs to treat both common and rare diseases is an attractive strategy because it identifies new uses of low-risk compounds that are outside the scope of the original medical indication. This strategy brings various advantages regarding the development of entirely new drugs for a given indication, owing to significantly lower overall research costs and shorter development timelines.⁵ It has been estimated that approximately 9,000 drugs are off patent and available for such investigation.

Logically, repurposing known drugs for COVID-19 may be first considered from pharmacologic agents with proven efficacy against other highly pathogenic viral infections, closely related to COVID-19, including the two deadly SARS-CoV-2 predecessors (severe respiratory syndrome coronavirus [SARS-CoV]⁶ and Middle East respiratory syndrome coronavirus [MERS-CoV]⁷) as well as severe influenza and community-acquired pneumonia.⁸ Useful medicines could also be identified from nononitropic agents.

In relation to COVID-19, pharmacologic agents can be divided into two categories: (1) Molecules that can directly target the viral replication and (2) Drugs that can act by either boosting the innate host antiviral immunity or by decreasing the pathologic inflammatory response⁹ that presumably leads to tissue damage and acute respiratory distress syndrome (ARDS) in COVID-19, SARS, and MERS.

At the time of this writing, an initial review of the ClinicalTrials website¹⁰ indicates there are 2,634 ongoing clinical trials with the goal of finding a promising drug for the treatment of COVID-19. In August 2020, the ClinicalTrials website¹⁰ reported 832 trials in phase II, 476 trials in phase III, and 105 trials in phase IV.

Most of these studies are focusing on the possibility of repurposing well-established drugs to combat COVID-19. Some of these trials are investigating medications that have been widely used to treat dermatologic indications for decades, posing the following questions: (1) do we as dermatologists have the “magic bullet” to fight COVID-19 in our therapeutic armamentarium? And (2) will the repurposing of dermatologic medications remain a fiction?

**From the clinics to the “cytokine storm”**

SARS-CoV-2 belongs to the genus beta coronaviruses of the Coronaviridae family of RNA viruses. It is also the seventh species of pathogenic human respiratory coronaviruses.¹¹,¹² Recognized since 1930, coronaviruses typically cause common cold symptoms, but SARS-CoV, MERS-CoV, and SARS-CoV-2 have caused severe pneumonia, respiratory failure, and death.¹³,¹⁴ The amino acid
sequence of SARS-CoV-2 proteins has between 95% and 100% similarity with those of SARS-CoV.15

Coronaviruses rely on their spike - proteins for binding to the host cell surface receptor during host cell entry.12 Phylogenetic studies have reported that SARS-CoV-2 has 76% similarity in the spike protein sequence with SARS-CoV, including 73% homology in its receptor-binding domain. It is also suggested that both viruses could use angiotensin converting enzyme 2 (ACE2) as a receptor to penetrate human cells.

Early in the COVID-19 pandemic, it became clear that the clinical presentation of SARS-CoV-2 infection varies from asymptomatic or mild illness (more often in children and young adults) to severe, critical, and potentially fatal forms, especially in older persons.16 Symptomatic patients usually present with fever, fatigue, and dry cough accompanied by other manifestations such as headache, nasal congestion, sore throat, myalgia, and arthralgia. At this early stage of the disease, the application of a broad spectrum of antivirals, antiretrovirals, antimalarials, antimicrobials, or even antiparasitic drugs may be of interest.17

Approximately 15% to 20% of patients may progress to shortness of breath, hypoxemia, and central nervous system disorders, leading to multiple organ failure. In more severe or critically ill cases, the infection causes bilateral pneumonia with severe complications such as ARDS (requiring oxygen assistance18), septic shock, plus acute cardiac or kidney injury.19

This severe group demonstrates a high mortality rate and is associated with patients who are older and have comorbidities, including diabetes, cardiovascular diseases, or malignancies.20 Clinical observations have shown that the exacerbation of the disease and death of patients who have COVID-19 are closely related to the inflammatory storm caused by overactivation of T cells, increased CCR4+CCR6+ Th17, and high cytotoxicity of CD8+ T cells in the peripheral blood.21 The affliction of the lower airways in severe COVID-19 seems to be driven by an uncontrolled immune-mediated inflammatory process similar to the one observed in rheumatic diseases with subsequent exhaustion of the immune response.22,23 SARS-CoV-2 activates both the innate and the adaptive immunity in the alveolar tissue. T cells trigger an excessive production of proinflammatory cytokines. The profile of this cytokine storm is characterized by increased levels of interleukin (IL)-1 β, IL-2, IL-6, IL-7, IL-8, IL-10, granulocyte-colony stimulating factor, interferon-γ inducible protein 10, monocyte chemoattractant peptide 1, macrophage inflammatory protein 1-α, and tumor necrosis factor (TNF)-α.24,25

Serum levels of IL-6 are reported as predictive for the severity of the SARS-CoV-2 pneumonia. The suppression of IL-6 has been effective in a variety of inflammatory diseases, including those of viral origin.26,27 At the stage of the cytokine storm, antinflammatory and immunosuppressive drugs—steroids, intravenous immunoglobulins (including monoclonal antibodies such as tocilizumab, adalimumab, janus kinase inhibitors, etc)—may reduce mortality rates.17

Repurposing of dermatologic medications to treat COVID-19

A great number of skin diseases indicate some internal disorders, the clinical presentation of which may be subtle or protean, and therefore, skin signs may serve as diagnostic evidence.28 Several inflammatory, autoinflammatory, and autoimmune dermatoses, namely psoriasis and atopic dermatitis, have been recognized as types of systemic diseases.29,30 Decades of major advances have revealed that a number of immune and nonimmune cells and those secreted by them—proinflammatory cytokines and chemokines—play a role in the pathogenesis of these diseases and in modulating chronic inflammation. Dermatologists have extensive experience with several agents that have either demonstrated promising in vitro antiviral action (directly targeting the viral replication) or appear to be effective in controlling the hyperimmune phenomenon, known as the cytokine storm in COVID-19-related ARDS. These include the wide range of biologic agents currently used in chronic inflammatory dermatoses to neutralize the proinflammatory cytokines or their receptors—ILs, TNF-α, and so on, (ie, the same molecules implicated in ARDS). The following challenging dermatologic conditions are also regarded as manifestations of the cytokine storm: (1) the Jarish-Herxheimer reaction during the initiation of antibiotic treatment for syphilis or relapsing fever21 and (2) Erythema nodosum leprosum in lepromatous leprosy. These conditions require control of the hyperinflammatory state with medications that are well established in the dermatologic armamentarium but unfamiliar to other specialties.

Well-established dermatologic drugs may offer an important opportunity for treatment, although further evaluation is indicated. We have reviewed several candidates for possible repurposing for treating COVID-19.

Synthetic antimalarial drugs

Chloroquine (CQ) and its less-toxic derivative hydroxychloroquine (HCQ) are synthetic antimalarials (SAMs) that have been widely used in dermatology for decades owing to their pronounced immunomodulatory effect. SAMs were introduced in 1930 as antimalarial agents to replace quinine, a natural compound derived from the bark of the cinchona tree.32 Currently, apart from their antiprotozoal activity, SAMs are well known as first-line or adjuvant drugs in the treatment of several inflammatory dermatoses and connective tissue diseases (Table 1).

For almost a century, SAMs have been widely used in dermatology. HCQ is currently considered a first-line treatment for cutaneous lupus erythematosus,33-35 but dose reduction was recently suggested (recommended daily dosage of 400 mg) to limit its potential side effects, particularly its ocular toxicity.33
SAMs are attractive drugs for repurposing owing to their affordable price and acceptable safety profile. The in vitro antiviral activity of CQ was identified more than 50 years ago. After the release of these preliminary in vitro data, SAMs received substantial international scientific and media attention in the fight against SARS-CoV-2. Hundreds of clinical trials have been launched globally to investigate their clinical effectiveness as monotherapy or in combination with azithromycin or favipiravir, as well as to determine their appropriate regimen in treating patients with COVID-19.

Chinese clinical trials have reported on the efficacy of CQ against COVID-19–associated pneumonia, and the drug has been included in the Guidelines for the Prevention, Diagnosis, and Treatment of Pneumonia Caused by COVID-19. A pilot observational study from France demonstrated that HCQ reduced viral load in most COVID-19 patients and that its efficacy was enhanced in combination with azithromycin. HCQ could be administered early in the COVID-19 course to prevent the spread of the infection or in the late stages during the cytokine storm. Some reports have suggested that HQC may modulate and balance the immunity through unknown mechanisms. In addition, HCQ has been reported to have antithrombotic, antifibrotic, antidiyslipidemic, and antihyperglycemic activity.

Side effects are exceedingly rare and include the following: dose-dependent retinopathy, gastrointestinal symptoms, cutaneous adverse reactions, worsening of psoriasis, hepatotoxicity, renal failure, myopathy, agranulocytosis, and potentially fatal cardiac arrhythmia in patients with a prolonged QT interval, bradycardia, low serum potassium, or low serum magnesium. The risk of arrhythmia may increase in cases of combined use of HCQ with several agents, including azithromycin, owing to the accumulation of their common side effect—cardiac arrhythmia in patients with preexisting QT interval prolongation.

In light of these early results, in March 2020 the FDA issued an Emergency Use Authorization to allow HCQ and CQ phosphate to be distributed and used for hospitalized COVID-19 patients. Concomitantly, the reputation of SAMs as effective drugs against COVID-19 was increasing both in the medical literature and in the media, which led to their shortage, thus complicating the treatment of patients with rheumatic and dermatologic diseases who were treated with CQ and HCQ at that time.

Unfortunately, more recent data, published several months after the COVID-19 outbreak, indicated that the use of CQ and HCQ is not so beneficial. A systematic review, including 3 randomized controlled trials (RCTs), 1 non-randomized trial, and 25 observational studies on the use of HCQ as monotherapy or in combination with azithromycin, reported no effect on the overall mortality from COVID-19. Several authors reported no significant association between HCQ administration and intubation or death. These results are in accord with a large RCT on HCQ performed by the RECOVERY Collaborative Group who observed less probability of being discharged alive from hospital within 4 weeks with HCQ and a higher frequency of invasive mechanical ventilation or death. An observational study on the clinical course of COVID-19 infection in

### Table 1 Therapeutic indications of SAMs

| Group disorders                              | Indication                                                      |
|----------------------------------------------|-----------------------------------------------------------------|
| Connective tissue disorders                  | Discoid lupus erythematosus                                     |
| Photodermatoses/photosensitivity disorders   | Subacute cutaneous lupus erythematosus                          |
| Inflammatory/autoimmune/allergic disorders   | Systemic lupus erythematosus                                    |
| Miscellaneous                                | Primary Sjogren syndrome                                        |
|                                              | Morphea                                                         |
|                                              | Systemic sclerosis                                               |
|                                              | Dermatomyositis                                                 |
|                                              | Eosinophilic fasciitis                                          |
|                                              | Reticular erythematous mucinosis                                 |
|                                              | Polymorphic light eruption                                       |
|                                              | Actinic prurigo                                                 |
|                                              | Chronic actinic dermatitis                                       |
|                                              | Solar urticarial                                                |
|                                              | Hidroa vacciniforme                                             |
|                                              | Porphyria cutanea tarda                                         |
|                                              | Rosacea                                                        |
|                                              | Lichen ruber planus                                             |
|                                              | Lichen planopilaris                                             |
|                                              | Actinic lichen planus                                           |
|                                              | Frontal fibrosing alopecia                                       |
|                                              | Granuloma annulare                                              |
|                                              | Sarcoidosis                                                     |
|                                              | Urticarial vasculitis                                           |
|                                              | Pemphigus foliaceus                                             |
|                                              | Lichen sclerosus                                                |
|                                              | Erythema nodosum                                                |
|                                              | Cutaneous CD8+ pleomorphic                                      |
|                                              | T-cell lymphoma                                                 |
|                                              | Hypercalcemia                                                   |
|                                              | Human immunodeficiency virus                                    |
|                                              | type I infection                                                |

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**SARS-CoV,** also accumulate early ago. Antiviral affordable Repurposing Inflammatory/toll-like SAMs allergic photosensitivity disorders 36 prevent (auto) the activity replication and, CQ thus the receptors type II (auto) antigen presentation. They inhibit the binding of toll-like receptors 7 and 9 to the respective ligands (DNA, RNA), the type I interferon response, and the synthesis of several cytokines (IL-1, TNF, IL-6), and chemokines. SAMs also prevent the glycosylation of ACE2 cellular receptor of SARS-CoV, thus inhibiting virus entry into the cell. 39
patients with systemic lupus erythematosus on long-term HCQ therapy (median 7.5 years) concluded that HCQ does not appear to prevent severe COVID-19 infection; the severe course of the disease in the researched group, however, may also be attributable to the high rate of comorbidities (obesity and chronic kidney disease).

These data marked the beginning of the period of skepticism in the repurposing of SAMs for COVID-19 treatment. On the basis of newer results, it is now considered unlikely that CQ and HCQ are effective in treating COVID-19. The FDA has revoked their authorizations, and the European Medicines Agency continues to recommend CQ and HCQ in the context of COVID-19 only in clinical trials or within national emergency use programs.

Despite these recent data indicating a sort of requiem for the use of SAMs for the treatment of COVID-19, other antimalarial compounds—pyroniridine, mefloquine, and artemisinin—have shown in vitro antiviral effects against SARS-CoV-2 and demonstrated antiinflammatory effects via IL-6–mediated pathways in other disease states. These observations suggest that SAMs may be suitable for repurposing during the current pandemic.

**Dapsone**

It has been hypothesized that the sulfone medication dapsone could be considered a treatment adjunct in ARDS. Currently, there are no biologic or clinical data or results from RCTs or case reports to provide evidence in support of the benefit of dapsone repurposing for the novel coronavirus infection.

Dapsone (4,4’-diaminodiphenylsulfone) was first administered to humans as an antileprous agent in 1945 and 1949, when it was used parenterally and orally, respectively. Around the same time, it was empirically observed that patients with acne fulminans significantly improved while taking dapsone for 3 to 4 months. Simultaneously, dapsone was first reported to be effective in dermatitis herpetiformis, considered (erroneously at that time) to be caused by bacterial allergy. This marked the beginning of its widespread application in dermatology.

Dapsone is currently used as an antinfective agent worldwide for the prevention and treatment of leprosy. It is also used for treating pneumocystis pneumonia in patients with HIV.

Apart from its antimycobacterial activity, dapsone is much more valuable in dermatology owing to its ability to inhibit the chemotaxis of polymorphonuclear leukocytes and to treat a broad list of neutrophilic dermatoses, plus many other inflammatory and autoimmune diseases of the skin. Dapsone is the first-line medication for treatment of dermatitis herpetiformis and bullous systemic lupus erythematosus.

Dapsone inhibits the migration of neutrophils to areas of inflammation in many ways but mainly through suppression of the release of IL-8, a potent chemokine secreted by keratinocytes, lung epithelium, monocytes, and macrophages. It also inhibits the neutrophil activation and degranulation after various stimuli, blocks the keratinocyte synthesis of IL-8, and reduces the neutrophil rolling and adhesion to the venular wall. In a therapeutic concentration, it inhibits the bullous pemphigoid immunoglobulin (Ig)G-mediated IL-8 release from cultured normal human epidermal keratinocytes without influencing the basal IL-8 level.

Dapsone inhibits the IL-8 secretion from normal human bronchial epithelial cells stimulated with lipopolysaccharide. It does not have any effect on the basal unstimulated IL-8 level. These data indicate that dapsone impairs neutrophil chemotaxis only at the sites of inflammation, apparently without impairing the innate immune response and increasing the risk of opportunistic infections. The crucial role of neutrophils in ARDS is confirmed by a comparative study of bronchoalveolar lavage early and a second one later in the course of ARDS, in which a reduction in neutrophils in the second lavage predicted survival, whereas a lack of reduction resulted in death.

During the initial stage of the fatal course of COVID-19, apart from the rapid replication of SARS-CoV-2, the immunopathologic process is likely to be initiated by the predominant induction of chemokines in lung tissues, which begin to recruit innate and adaptive immune cells to lung lesions. In patients with severe COVID-19–associated pneumonia or ARDS, there is increased pulmonary inflammation with infiltration of neutrophils and macrophages at the site of injury, thick mucus secretions in the airways, elevated levels of serum proinflammatory cytokines, including IL-8, extensive lung damage, and microthromboses. Capsone can control the increased secretion of IL-8 and the resulting neutrophilic inflammation in COVID-19–related ARDS.

Some combinations of dapsone, either with doxycycline or with colchicine and the antipsychotic drug olanzapine, have been suggested as hypothetic therapeutic options that should be regarded with caution. In addition, dapsone has been observed to act as a competitor of inflammasome and, as such, may be effective against COVID-19. Inflammasomes are large intracellular multiprotein complexes that play a central role in innate immunity. Their activation has been reported to play a role in the pathogenesis of several inflammatory and infectious diseases, including SARS-CoV and SARS-CoV-2 infections. Upon metabolic activation, dapsone is competing covalently with proteins that activate the nucleotide-binding oligomerization domain-like receptor pyrin domain-containing (NLRP3) inflammasome, the overactivation of which contributes to the pathogenesis of cardiometabolic disorders and plays a pivotal role in the pathophysiology of either obesity or diabetes. This, in turn, somewhat explains the idiosyncratic reactions characterizing dapsone hypersensitivity syndrome, a severe adverse reaction showing many clinical manifestations similar to those observed in severe COVID-19.
The possible efficacy of dapsone in COVID-19 should be supported by additional RCTs.

**Colchicine**

Colchicine is an alkaloid obtained from the flowers and seeds of the autumn crocus (Colchicum autumnale). This is an old drug used for centuries for its effect on joint swelling and, since the 16th century, as an antitoxic medication. Some studies have reported that colchicine has additional antimicrobial properties that are based on its property to bind to the microtubule proteins and, in this way, to interfere with the mitotic spindle activity to interrupt the mitosis. Colchicine is known to increase the intracellular cyclic adenosine monophosphate, resulting in suppression of leukocyte function. In addition, the drug impairs the chemotaxis, migration, and phagocytic capability of polymorphonuclear leukocytes. The degranulation of mast cells can also be interrupted by colchicine.

Dermatologists are familiar with colchicine because it is used for a variety of dermatologic indications as a systemic treatment or for topical application (Table 2).

The optimal dosage of colchicine for dermatologic indications should be 0.5 to 2.0 mg daily, dosed once a day, twice a day, or three times a day. Long-term studies on the use of colchicine at a dosage of 1.0 to 2.0 mg daily for patients with familial Mediterranean fever have confirmed that the drug has a good safety profile with prolonged use.

Although colchicine is effective, several side effects have been reported, including agranulocytosis and aplastic anemia, which may be potentially fatal, especially with overdosing. Coagulopathy and neuromuscular disturbances are also known side effects of colchicine. Minor side effects consist of abdominal pain, nausea, and vomiting. When applied topically, local reactions, such as erythema, vesication, and crusts, may appear.

The justification for the use of colchicine in the combat against COVID-19 may be its antiviral properties. Colchicine is known to inhibit the microtubule polymerization within the cell. Because the intracellular transport of viral particles in the host cell depends on the microtubule network, the tubulin ligands potentially inhibit the viral replication. Coronaviruses, such as SARS-CoV-2, can induce an uncontrolled cytokine and chemokine response. Patients with severe COVID-19 exhibit higher serum levels of proinflammatory cytokines (TNF-α, IL-1, and IL-6) and chemokines (IL-8) in comparison with individuals with mild disease or healthy controls. Colchicine is known to decrease the production of proinflammatory cytokines, such as IL-1, IL-6, and TNF-α.

Additional studies have shown that viroporin E, a component of SARS-CoV, forms Ca$^{2+}$-permeable ion channels and activates the NLRP3 inflammasome. In addition, another viroporin 3a is found to induce NLRP3 inflammasome activation through unclear mechanisms, which is observed in COVID-19. Colchicine counteracts the assembly of the NLRP3 inflammasome, thereby reducing the release of IL-1 and an array of other ILs, including IL-6, that are formed in response to danger signals.

Several clinical studies have reported promising results on colchicine treatment of patients who have COVID-19. A case series has demonstrated a favorable outcome from a loading dose of 1.0-mg oral colchicine 12 hours apart, followed by 1.0-mg daily colchicine until the third day of axillary temperature <37.5°C (99.5°F). The treatment led to defervescent within 72 hours in all 9 treated patients.

GRECCO-19 is a prospective, randomized, open-label, controlled study to assess the effects of colchicine in COVID-19 for the prevention of complications. In addition to the usual medical treatment, a loading dose (per orally) of colchicine 1.5 mg (followed 60 minutes later by 0.5 mg if no adverse gastrointestinal effects are observed) is administered followed by 0.5-mg colchicine twice a day (except for patients weighting <60 kg in whom 0.5-mg colchicine should be administered once daily). Results indicate that participants who received colchicine had statistically significant reduced time to clinical deterioration compared with the control group who did not receive colchicine. Along with the GRECCO-19 trial, there are currently 25 registered studies that will provide relevant clinical data to support the use of colchicine in COVID-19 patients.

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**Table 2: Dermatologic indications of colchicine**

| Group disorders                      | Indication                                      |
|--------------------------------------|-------------------------------------------------|
| Neutrophilic dermatoses              | • Sweet syndrome                                |
|                                      | • Pyoderma gangrenosum                          |
|                                      | • Subcorneal pustular dermatosis                |
| Acne and related disorders           | • Acne                                          |
|                                      | • Hidradenitis suppurativa                       |
| Autoimmune bullous diseases          | • Dermatitis herpetiformis                      |
|                                      | • Epidermolysis bullosa aquisita                |
|                                      | • Mucous membrane pemphigoid                    |
|                                      | • Linear IgA dermatosis                         |
| Psoriasis                            | • Plaque-type psoriasis                          |
|                                      | • Palmoplantar pustulosis                       |
| Vasculitides                         | • Cutaneous vasculitis                          |
|                                      | • Urticarial vasculitis                         |
|                                      | • Schamberg disease                             |
| Aphthoses                            | • Behçet syndrome                               |
|                                      | • Recurrent aphthous stomatitis                 |
| Benign and premalignant skin tumors  | • Actinic keratoses (topical application)       |
|                                      | • Condylomata acuminata (topical application)   |

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Although colchicine has been used for centuries, it is still being explored for various dermatological conditions. Its efficacy in COVID-19 highlights the potential of repurposing existing medications for new indications.
**Table 3** Dermatologic indications of ivermectin

| Systemic use   | Topical use                  |
|----------------|------------------------------|
| Scabies, crusted scabies | Larva migrans                |
| Demodiosis      | Filariaisis                  |
| Filariasis      | Loasis                       |
| Onchocerciasis  | Toxocarosis                  |
| Scabies         | Rosacea                      |
| Scabies         | Myiasis                      |
| Rosacea         | Pediculosis                  |

**Ivermectin**

Ivermectin is an avermectin acaricide agent used for several decades to treat a variety of infectious diseases in mammals and in humans. It may be a candidate for the treatment of COVID-19. Owing to its broad-spectrum antiparasitic activity against a range of nematodes and ectoparasites and its good safety profile upon oral intake, ivermectin was approved by the FDA in 1996. It has played a key role in the elimination of onchocerciasis and strongyloidiasis, as well as in the treatment of ascariasis, trichiniasis, filariasis, and enterobiasis. It is also applied worldwide in veterinary practice to control infestation with sarcoptic mites in domestic animals (Table 3).

Ivermectin is used in dermatology for the systemic and topical treatment of the most common ectoparasitic infestations, such as scabies, pediculosis, and demodiosis. It works by interrupting the functioning of a class of ligand-gated chloride ion channels in the scabies mite, causing persistent channel opening and prolonged secretion of gamma-aminobutyric acid, which leads to death of the parasite. During more than 4 decades, ivermectin has proven to be a safe and effective treatment for scabies, although the FDA has not approved it for this use. Oral ivermectin is the first-line treatment for crusted scabies. Ivermectin is also the treatment of choice in patients refractory to standard topical therapies, such as those with HIV/AIDS, endemic scabies in the community, or in nursing home settings, as well as in patients who are allergic to permethrins or severely irritated by topical benzyl benzoate.

The recommended dosage of oral ivermectin in “classic” scabies is 200 μg/kg, twice in week intervals (7 days apart); whereas in crusted scabies multiple oral doses of 200 μg/kg are administered on days 1, 2, and 8 in conjunction with topical scabicides and keratolytics. Ivermectin is also active when applied topically on the skin. In 2012, the FDA approved topical ivermectin 0.5% lotion for treatment of head lice in patients aged 6 months and older. Based on its dual antiflamatory and antiparasitic action against demodex mites, topical 1.0% ivermectin cream was approved 2 years later for the treatment of rosacea and has since been widely used in patients with the papulopustular forms of the disease.

*In vitro* and *in vivo* data indicate that ivermectin also has potent broad-spectrum antiviral properties against several RNA and DNA viruses. Its antiviral potential against RNA viruses is attributed to its ability to specifically inhibit importin (IMP) α/β1-receptor responsible for the transmission of viral proteins into the nucleus of the host cell. Ivermectin destabilizes IMPα/β1, which results in a blockade of the nuclear transport of viral proteins.

Because SARS-CoV-2 is a single-stranded positive sense RNA virus, a similar mechanism of action of ivermectin via binding to IMPα/β1 is expected to be operating in COVID-19. A recent preclinical study from Australia demonstrated that the single application of 5.0 μM ivermectin to Vero/hSLAM cells (*in vitro*) 2 hours after infection with the SARS-CoV-2 isolate, reduced the SARS-CoV-2 viral RNA by almost 5,000-fold within 48 hours.

Despite these promising results, pharmacokinetic analysis has provoked a great deal of skepticism about the *in vivo* success of ivermectin in COVID-19 because its plasma levels after oral administration—in the dosages applicable for treatment of parasitic diseases in humans—are much lower than the concentration demonstrated to inhibit viral replication in vitro (ie, 5.0 μM).

A preprint, first posted but later retracted, reported on the clinical benefit of ivermectin in 1,408 critically ill COVID-19 patients. A dramatic survival difference was declared between patients (n = 704) who were treated with ivermectin 150.0 mcg/kg following initiation of mechanical ventilation and similarly ill patients (n = 704) who received therapy without ivermectin.

Another preprint report on an observational retrospective cohort study of 280 consecutive patients with COVID-19 hospitalized in south Florida in the United States demonstrated significantly lower mortality rates in those who received at least 1 dose of ivermectin compared with usual care. Mortality was also lower among 75 patients with severe pulmonary disease treated with ivermectin, but there was no significant difference in successful extubation rates.

Based on a review paper by the Pan American Health Organization regarding all COVID-19 laboratory and clinical human studies published from January to May 2020, concern was expressed that those on ivermectin might have a high risk of bias and that insufficient evidence existed to draw a conclusion on the benefits and harms of the drug. Recommendations regarding the use of ivermectin as a treatment for COVID-19 were elaborated, encouraging the use of unproven therapies, including ivermectin, only in the context of RCTs.

A phase-III, double-blind RCT has been begun with the aim of determining the safety and efficacy profile of the combination therapy of hydroxychloroquine and ivermectin in the treatment of hospitalized COVID-19 patients.
Globally, according to information available at www.clinicaltrials.gov on December 3, 2020, a total of 44 clinical trials on ivermectin in COVID-19 are listed, of which 11 have been completed. Ivermectin is being investigated in oral or parenteral forms and as a nasal spray. Investigational treatment regimens include the addition of ivermectin to a standard anti-COVID-19 protocol (eg, hydroxychloroquine plus favipiravir and azithromycin), or ivermectin in combination with doxycycline. An interesting, completed trial with unpublished results investigated the topical use of ivermectin to prevent infection with SARS-CoV-2.

In one retrospective study, ivermectin application was associated with significantly reduced mortality compared with patients at the same hospitals not receiving ivermectin, particularly in cases with severe pulmonary disease. Additional in vitro and in vivo studies and evaluation in RCTs are needed to validate the role of ivermectin in the management of COVID-19, especially in critically ill patients. The hope is that ivermectin in COVID-19 will not repeat its unfortunate Zika results from 2016 in which the drug’s promising antiviral activity in vitro failed to be confirmed in vivo.

**Cyclosporine**

Cyclosporin A (CsA) is an FDA-approved drug (1983) isolated from the fungus *Beaveria nivea*. Its main therapeutic indication is to prevent organ rejection in transplanted patients. In dermatology, CsA is used to treat T cell-associated autoimmune diseases, such as Behçet disease, psoriasis (including psoriatic arthritis), and lupus erythematosus. CsA has immunosuppressive and antiinflammatory properties attributable to its ability to inhibit the transcription of genes required for T cell proliferation (including genes for IL-2).

On the other hand, IL-2 is reported as a potential trigger of the cytokine storm in severe COVID-19. SARS-CoV nsp1 induces the expression of IL-2 via activation of nuclear factor of activated T cell.

CsA has anticonviral action against all genera, including SARS-CoV. Its anti-CoV action is mediated by the inhibition of cyclophilin-A-dependent viral assembly, as well as inhibition of the nuclear factor of activated T cell pathway or even by genetic or pharmacologic-specific inhibition of cyclophilin-D, complicating the viral replication. Owing to the high similarity between SARS-CoV and SARS-CoV-2 (79.5% sequence identity), it is presumed that CsA will have similar pharmacologic anti-SARS-CoV-2 properties.

There is a question as to whether CsA may increase the ACE2 shedding and thus potentiate the SARS-CoV-2 infection. Preclinical studies are necessary to demonstrate whether the use of cyclosporine in SARS-CoV-2 infection is beneficial or harmful. An additional concern is the potential serious side effects of CsA, which include hyperlipidemia, gingival hyperplasia, nausea, vomiting, abdominal pain, headache, susceptibility to infections, triggering of cancer development, blood pressure increase, nephrotoxicity, and immune suppression.

Clinical data on the effect of CsA in COVID-19 are sparse. Some investigators have suggested that the administration of the drug in patients who have had a kidney transplant is beneficial both in the early viral phase of COVID-19, as well as in combating the cytokine release syndrome in severe disease. Patients who receive CsA for dermatologic autoimmune diseases may benefit from their treatment in case of COVID19 infection.

Currently, there are eight registered ongoing clinical studies on the use of CsA in COVID-19 patients. Two studies investigate the effectiveness of CsA either alone or in combination with low-potency steroid in COVID-19 pneumonia. Another study focuses on evaluating the usefulness of topical CsA in COVID-related keratoconjunctivitis. One clinical trial compares the clinical course of COVID-19 in patients who have had a transplant who either interrupt or continue their immunosuppressive therapy. Results from those studies have not yet been released.

**Thalidomide**

Despite its negative reputation during the early 1960s, thalidomide has a place among the drugs being tested as a potential treatment for COVID-19. Originally used as an antiemetic agent in pregnancy and withdrawn from the market due to its teratogenic effects, thalidomide has been rehabilitated and reintroduced in clinical practice owing to its immunomodulatory, antifibrotic, and antiinflammatory properties. It currently has FDA approval for the treatment of erythema nodosum lepromus and multiple myeloma.

Because it has been classified as an orphan drug, thalidomide has been used off-label to treat numerous autoimmune and inflammatory dermatologic diseases refractory to traditional treatments, including severe recurrent aphthous stomatitis, Behçet’s syndrome, discoid lupus erythematosis, prurigo nodularis, actinic prurigo, uremic pruritus, erythema multiforme, cutaneous graft versus host disease, sarcoidosis, pyoderma gangrenosum, lichen planus, Jessner’s lymphocytic infiltration, Langerhans-cell histiocytosis, polymorphic light eruption, cutaneous fibrosis in systemic scleroderma, and—on one occasion—dermatomyositis. Thalidomide has been continuously investigated for the treatment of HIV-related mouth and throat ulcers and HIV-related weight loss and body wasting. Outside of the dermatology field, thalidomide is used as an immunomodulatory agent in rheumatoid arthritis, inflammatory bowel disease, solid tumors, hematologic malignancies, heart failure, pulmonary fibrosis, and ophthalmopathies.

Thalidomide is a derivative of glutamic acid, containing a right-sided glutarimide ring mediating its hypnotic effects and a left-sided phthalimide ring believed to be responsible for its teratogenicity. After oral absorption, the peak plasma concentration is reached in 2.9 to 5.7 hours, with rapid
penetration of the hematoencephalic and placental barriers. Thalidomide is metabolized through spontaneous, nonenzymatic hydrolysis in blood and tissue and minimally by the hepatic cytochrome P450 system. Its half-life to elimination is 5.5 to 7.3 hours, and 92% is excreted in the urine, with less than 1% in its original form. Thalidomide is distributed under a special program, the “Thalidomide” Risk Evaluation and Mitigation Strategy, which requires prescribers, patients, and pharmacies to be certified by the program.

Although not fully elucidated, most of the biologic effects of thalidomide are related to its antiinflammatory, immunomodulatory, and antiangiogenic properties. Thalidomide impairs the synthesis of TNF-α and increases peripheral blood CD8+ T cells, plasma IL-12 levels, interferon-γ, and cytotoxic activity. In vitro and in vivo studies have revealed that thalidomide leads to decreased expression of IL-1 β and IL-6 in human lung epithelium, thus contributing to the attenuation of pulmonary fibrosis, oxidative stress, and inflammation. Thalidomide also interferes with integrin expression, decreases circulating helper T cells and inhibits angiogenesis. Preclinical data indicate that, in mice, thalidomide may attenuate pulmonary injury induced by influenza A (H1N1) virus, decrease the production of inflammatory and fibrogenic cytokines (TNF-α, IL-1β, IL-6, TGF-β1, myeloperoxidase, nitric oxide, and hydroxyproline) in paraquat-induced pulmonary fibrosis, and decrease inflammation.

Thalidomide has been reported to successfully control the symptoms of immune reconstitution inflammatory syndrome in HIV-infected patients, which is observed in up to 35% of patients after beginning antiretroviral therapy. Immune reconstitution inflammatory syndrome is characterized by paradoxical deterioration caused by immune dysregulation, cytokine storm, and limited effector T-cell function.

The hyperinflammatory cytokine storm in severely or critically ill patients is the major underlying cause explaining much of the morbidity and mortality of SARS-CoV-2 infection. Given that thalidomide is used to treat lepra reactions, a similar hyperinflammatory phenomenon in lepromatous leprosy, its administration to prevent or treat COVID-19 cytokine storm should be considered, except for women of childbearing potential. The oral intake of thalidomide and its safety profile upon short-term application have been considered as good reasons for its use in SARS-CoV-2 infected patients.

The beneficial effect of thalidomide (100 mg orally once daily) in combination with low dose corticosteroid (40-mg methylprednisolone intravenously) was reported in a 45-year-old woman hospitalized for COVID-19. Her state rapidly deteriorated on day two of her hospital stay, indicating the occurrence of a cytokine surge and inappropriate immune response; after this treatment, a substantial reduction of the pulmonary effusion and the elevated serum inflammatory cytokines (IL-6, IL-10, and IFN-gamma) was achieved and lymphopenia was stemmed.

Despite the lack of additional data on the effect of thalidomide on SARS-CoV-2, these theoretic and positive clinical results (although only from one reported patient) are a promising background to hypothesize that thalidomide may be beneficial to control the clinical manifestations of pulmonary involvement and the cytokine release syndrome in COVID-19. The answer to this clinical dilemma, however, lies in future RCTs. Two clinical trials are currently planned to assess the efficacy and safety of thalidomide in severe COVID-19 patients in China.

Corticosteroids/dexamethasone

Since their introduction into clinical practice in the 1950s, systemic corticosteroids (SCs) have played a major role in dermatologic therapy owing to their potent immunosuppressive and antiinflammatory properties. They are the mainstay of treatment of a number of autoimmune, inflammatory, autoinflammatory, and allergic dermatoses, including life-threatening blistering diseases such as pemphigus and pemphigoid, connective tissue disorders, neutrophilic dermatoses, vasculitis, and sarcoidosis.

Since the COVID-19 pandemic began, patients receiving SCs for cutaneous disease have been considered a potentially vulnerable population that requires specialized care and advice during the COVID-19 pandemic. The Australia/New Zealand consensus statement on the use of immunomodulatory and biologic agents for severe cutaneous disease in times of COVID-19, outlines the following recommendations regarding the use of SCs during the COVID-19 pandemic:

- Dosage exceeding a 20-mg prednisolone equivalent is regarded as significantly immunosuppressive and long-term usage should be avoided.
- Use of prednisolone 15 mg or higher for longer than 3 weeks is associated with adrenal axis suppression.
- Sudden cessation or significant dose reduction is inadvisable owing to the risk of adrenal insufficiency.
- If a reduction of corticosteroid therapy is indicated to mitigate infection risk during the pandemic, a graduated reduction is advised, aiming for a dose of ≤10 mg of prednisolone or equivalent.
- Corticosteroid therapy may need to be increased in times of physiologic stress including COVID-19, ARDS, and other serious infection.

Apart from the fears of a more complicated clinical course of COVID-19 in patients who receive SCs for other indications, there has been hope that SCs might prevent the worst complication in COVID-19: the ARDS.

Because the cause of death in COVID-19 is ARDS and organ failure attributable to the cytokine storm caused by hyperactivation of the host immune response, suppressing this process or preventing it should be considered at an early course of the disease. To achieve this, a short course of
low-dose steroids during an early COVID-19 stage may be administered, but it may not be effective in the later stages of the disease.

Early administration of SCs in viral infections may reduce the risk of ARDS. In the past, SCs have been used to reduce the immune-mediated inflammation in syndromes closely related to COVID-19, including SARS and MERS. Although the fear of viral replication does exist, provisional recommendations for managing excessive inflammatory response in COVID-19 include SCs.

The US National Institutes of Health has issued guidelines for treatment of COVID-19 patients that consider the use of SCs and especially dexamethasone. They recommend the following:

- Use dexamethasone (at a dose of 6 mg per day for up to 10 days) in patients with COVID-19 who are mechanically ventilated and in patients with COVID-19 who require supplemental oxygen but who are not mechanically ventilated.
- Avoid using dexamethasone in patients with COVID-19 who do not require supplemental oxygen.

These recommendations are based on results from a large, randomized, open-label trial suggesting that dexamethasone reduces mortality in hospitalized COVID-19 patients who require mechanical ventilation or supplemental oxygen (RECOVERY trial). Dexamethasone was administered as an oral (liquid or tablet) or intravenous preparation, at a dosage of 6 mg daily for 10 days, in one of the arms. In the group treated with dexamethasone, mortality was reduced by 35% in ventilated patients and by 20% amongst patients on supplemental oxygen therapy. No benefit was observed in milder cases.

Similar data have been published from an open-label non-randomized control trial, in which the group of critically ill patients with COVID-19 who received adjuvant SCs to the standard antiviral protocol SCs (median hydrocortisone equivalent dosage 200 mg daily), showed significantly reduced death incidence 5.4% compared to the non-steroid control group (52.3%). Other studies, however, contradicted the benefit of SCs use in COVID-19 patients without ARDS. Reported data showed that up to 70% of the critically ill patients received SCs. The results of another study revealed that the administration of SCs was related to a higher proportion of patients with symptoms of COVID-19 lasting for more than 10 days.

The US National Institutes of Health guidelines warn about adverse events and drug interactions in COVID-19 patients who receive dexamethasone. Close monitoring should be carried out for side effects of dexamethasone, such as hyperglycemia, secondary infections, glaucoma, cataract formation, fluid retention, hypertension, and psychiatric effects. Reactivation of latent infections (hepatitis B virus, herpesviruses, tuberculosis) could be a concern in case of prolonged SC administration.

Dexamethasone is generally safe and presents a favorable benefit-risk profile, particularly in patients with severe forms of pneumonia. As the treatment time is generally expected to be short, even at high doses, SCs are not associated with serious side effects. Worsening of preexisting diabetes and/or hyperglycemia is temporary. Prolonged use for more than 2 weeks may be associated with adverse events, such as psychological effects (eg, mood swings, memory issues, confusion, or irritation), weight gain, or increased risk of infections and osteoporosis.

The Italian Society of Endocrinology advises that the parenteral administration of high doses of methylprednisolone (eg, up to 8 mg/kg a day) or dexamethasone (eg, 20 mg a day for 5 days, then 10 mg a day for 5 days), requires a cautious dose tapering until the end of the acute phase of COVID-19 due to the risk of subsequent adrenal insufficiency. A systematic review of 5 studies (4 retrospective studies and 1 quasi-prospective study) evaluating the role of SCs demonstrated beneficial effect in 3 studies. The other 2 studies, however, reported no benefit, suggesting significant harm in critical cases in 1 sub-study.

A meta-analysis performed during the early months of the COVIC-19 pandemic studied the effect of SCs on the clinical course of SARS, MERS, and COVID-19. The analysis concluded that the corticosteroid use did not reduce mortality but was associated with increased hospitalization duration. No favorable impact of SCs has been reported regarding death, admission to intensive care unit, or mechanical ventilation.

The current interim guidance from the WHO on the clinical management of severe acute respiratory infection when COVID-19 is suspected advises against the use of corticosteroids unless indicated for another reason. The WHO recommends avoiding routine administration of SCs to patients with COVID-19 outside of clinical trials.

No uniform opinion exists regarding the use of SCs in patients with COVID-19. Administration of SCs should be individually tailored on the basis of the patient’s medical history and the severity of the disease.

**Isotretinoin**

Isotretinoin (13-cis-retinoic acid) is derived from vitamin A. Oral isotretinoin was developed in the 1950s as an anticancer drug, but its actual use began almost 20 years later. It was approved by the FDA for nodulocystic acne in 1982 and is currently the gold standard for treating severe and moderate nodulocystic acne, scarring acne, or acne resistant to long-term oral antimicrobials.

The daily dose of oral isotretinoin in acne varies from 0.5 to 1.0 mg/kg body weight. Treatment regimens usually begin at 0.5 mg/kg a day and may be increased to 1.0 mg/kg a day, but some centers initiate treatment at the higher dose that provides optimal benefit. A lower dose of isotretinoin, 10 mg per day, has been suggested for acne and for other indications.
Table 4  Dermatologic indications for the use of isotretinoin

| Primary indication | Disorders of the sebaceous glands and other skin appendages |
|--------------------|-----------------------------------------------------------|
|                    | • Acne                                                      |
|                    | • Rosacea                                                  |
|                    | • Seborrhoe                                                |
|                    | • Seborrhoehe dermatits                                   |
|                    | • Morbían disease                                          |
|                    | • Sebaceous hyperplasia                                    |
|                    | • Hidradenitis suppurativa                                 |
|                    | • Folliculitis decalvans                                  |
| Cutaneous malignancies and precancers | • Cutaneous T-cell lymphoma (CTCL) |
|                     | • Basal cell carcinoma                                     |
|                     | • Squamous cell carcinoma                                  |
|                     | • Keratoacanthoma                                          |
|                     | • Xeroderma pigmentosum                                   |
|                     | • Leukoplakia                                              |
|                     | • Actinic keratoses                                        |
|                     | • Actinic damage                                           |
| Disorders of keratinization | • Darier disease                                           |
|                        | • Grover disease                                           |
|                        | • Lamellar ichthyosis                                      |
|                        | • Galli-Galli disease                                      |
|                        | • Erythrokeratodermia variabilis Mendes da Costa           |
|                        | • Pityriasis rubra pilaris                                 |
|                        | • Confluent and reticulated papillomatosis of Gougerot-Carteaud |
|                        | • Kyrie disease                                            |
|                        | • Filiform porokeratosis                                   |
|                        | • Diffuse palmoplantar keratoderma (Vohwinkel syndrome)    |
| Other autoimmune and inflammatory dermatoses | • Psoriasis                                           |
|                                | • Discoid lupus erythematosus                              |
|                                | • Granuloma annulare                                       |
|                                | • Sarcoïdosis                                              |
|                                | • Lichen planopilaris                                      |
|                                | • Erythema dyschromicum perstans                           |
| Miscellaneous human papilloma virus infections | • Warts                                                  |
|                                      | • Condylomata acuminata                                   |
|                                      | • Epidermodysplasia verruciformis                         |

Isotretinoin has remarkable antiinflammatory, immunomodulatory, antineoplastic, antiandrogenic, antiangiogenic, and other pharmacologic properties, which have led to the use of the drug for treatment of a large number of dermatologic and non-dermatologic conditions, including more than 50 off-label uses (Table 4).148,150

A phase II study suggests the beneficial use of a combination of IL-2 and isotretinoin in minimal residual disease in metastatic solid tumors in complete remission after chemotherapy.151 Among the non-dermatologic indication of isotretinoin is neuroblastoma, for which it is used as adjuvant treatment.152

The main contraindication of isotretinoin is pregnancy because the drug has proven teratogenicity in approximately 1 in 10 drug-exposed pregnancies.153 Other common side effects include mucosal dryness, cheilitis, and conjunctivitis.154 Psychiatric disorders, such as depression, psychosis, suicidal tendency, and suicide, have been a potential but minimal drug-related concern,155 although these disorders are not confirmed by recently accumulated data.156

The rationale behind investigating isotretinoin as a candidate for drug repurposing against COVID-19 resides in the following four properties of the drug: (1) modulation of IL-2, interferon γ (IFN-γ) and T and B lymphocyte function,149 (2) down regulation of ACE2 receptors,157 which are essential for the viral entry into the host cell,158 (3) potential inhibition of papain-like protease (PLpro)-protein encoded by SARS-CoV-2 genes,159 and (4) increase of CD4 counts and marked decrease of viremia in HIV-positive patients.160

An interventional comparative phase III RCT for the use of isotretinoin in COVID-19 compares the efficacy of isotretinoin 0.5 mg/kg a day against the standard therapy (paracetamol 500 mg every 6 hours, hydroxychloroquine 500 mg every 12 hours, oseltamivir 150 mg every 12 hours for 5 days, azithromycin 1 g first day then 500 mg a day for first line or clarithromycin 500 mg every 12 hours for 7 to 14 days, ascorbic acid 500 mg every 12 hours and cyanocobalamin IV once daily plus 2 capsules of lopinavir 400 mg or ritonavir 100 mg twice daily in severe cases) and isotretinoin 0.25 mg/kg a day plus the standard therapy in COVID-19 patients.161

Currently, 8 registered clinical trials are aiming to assess the potential use of isotretinoin in COVID-19. They are in the prerecruitment phase, and clinical results are likely to be delayed.162

**Rituximab**

Rituximab is a chimeric IgG1 monoclonal antibody targeting CD20 (transmembrane protein expressed in B cells) causing B cell depletion. Its original indication is the treatment of large diffuse non-Hodgkin lymphoma and chronic lymphocytic leukemia.163 Based on the observation that concomitant autoimmune disorders improve in the course of rituximab administration, the drug has been repurposed for the treatment of a variety of hematologic, rheumatologic, and dermatologic diseases including systemic lupus erythematosus and pemphigus vulgaris.132

The potential role of rituximab in COVID-19 is based on preventing the immune phenomenon of the cytokine storm. Rituximab has the potential to downregulate the immune response by three known mechanisms: antibody dependent
cellular cytotoxicity, complement mediated cytotoxicity, and apoptosis.\textsuperscript{164}

Currently there are no registered ongoing studies for rituximab in COVID-19.\textsuperscript{10} Of note, there are concerns regarding rituximab in chronically treated patients who will potentially receive the SARS-CoV-2 vaccine. As a B-cell depleting agent, rituximab may interfere with the ability to produce an effective immune response, suggesting the need to extend dose intervals.\textsuperscript{165}

**High-dose intravenous immunoglobulins**

High-dose intravenous immunoglobulins (HD IVIGs) are used in a number of autoimmune dermatologic conditions including therapy-resistant life-threatening pemphigus vulgaris.

HD IVIGs have immunomodulatory properties that explain their potential benefit in the COVID-19 cytokine storm. The Kawasaki-like syndrome, which appears to be the pediatric analogue of the cytokine storm, should logically respond to therapies successfully applied against the original Kawasaki syndrome, such as HD IVIGs.\textsuperscript{132} In cases of COVID-19, the polyclonal IgG isolated from healthy donors can be further enhanced by using IgG antibodies from recovered COVID-19 patients in the same geographic region as the patient.\textsuperscript{166}

Single case reports support the positive effect of HD IVIGs in COVID-19,\textsuperscript{167} although there are currently no RCTs formally evaluating their effectiveness. According to recent studies, HD IVIGs are effective in the early stages of SARS-CoV-2 infection and can reduce the use of mechanical ventilation through prevention of the progression of pulmonary injury.\textsuperscript{168}

**Conclusions**

It is challenging to select the appropriate pharmacologic treatment when facing a rapidly evolving global health emergency like the COVID-19 pandemic. The literature is flooded with data on possible drug repurposing that could serve as a bridge to the time when new anti-SARS-CoV-2 medications will be developed. We have reviewed the existing data regarding the possible efficacy of dermatologic medications on the clinical course of COVID-19. Although some drugs used in dermatology have demonstrated efficacy, data are frequently controversial or inconclusive, and currently the sought-after miracle drug that will fight COVID-19 remains elusive.

**Conflict of Interest**

None.

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