Utility and risk of dermatologic medications during the COVID-19 pandemic

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Abstract
In the era of staggering speed in development of the novel coronavirus disease (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), we have reviewed the dermatologists' tools at hand for their utility (and potential risks) in patients affected by COVID-19. This review aims to shed light on the antiviral and proviral potential of drugs routinely used in dermatology to modulate COVID-19. The literature search included peer-reviewed articles published in the English language (clinical trials or scientific reviews). Studies were identified by searching electronic databases (MEDLINE and PubMed) from January 1990 to March 2020 and by reference lists of respective articles. Somewhat to our surprise, we have found that several of our drugs widely used in dermatology have antiviral potential. On the other hand, we also frequently use immunosuppressive drugs in our dermatologic patients that potentially pose them at increased risk for COVID-19.

KEYWORDS
COVID-19, dermatologic medications, pandemic

1 | INTRODUCTION
The global public health is currently challenged with the volcanic spread of coronavirus disease (COVID-19).1–3 The entire world is in the grip of the looming threat of this viral infection.4–6 The World Health Organization (WHO) declared it a health emergency and a pandemic.7,8 In light of the lack of evidence-based treatments for COVID-19, repurposing of available medications, including those used by dermatologists, should be considered. In this review, we have tried to evaluate the medications that are generally used in skin diseases (Table 1).

2 | SYSTEMIC MEDICATIONS
Complex interplay exists between viral replication and host immune response. Due to lack of specific data, more studies need to assess the risk of immunosuppression in patients with COVID-19.

2.1 | Chloroquine and hydroxychloroquine
Chloroquine (CQ), an antimalarial and autoimmune disease medication, has been found to fulfill several criteria of a broad-spectrum antiviral drug, including significant inhibition of viral infections that invade cells through the endosome pathway, inhibition of autophagy and interference with virus infection and replication.9 More specifically, and of great current interest, CQ has been demonstrated to possess strong antiviral effects on severe acute respiratory syndrome (SARS), the culprit of the Asian epidemic outbreak in 2003.10 The mechanism is sophisticated and of potential utility for COVID-19: CQ inhibits virus replication by decreasing terminal glycosylation of angiotensin-converting enzyme 2 (ACE2) receptors on the surface of SARS-CoV-infected Vero E6 cells, thus interfering with the binding of SARS-CoV to ACE2 receptors. These ACE2 receptors not only bind SARS-CoV, but also severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes COVID-19.10 In addition to its antiviral activity, CQ has an immune-modulating activity that may synergistically increase its antiviral effect.
After oral administration, CQ is quickly distributed in the body, including the lung. A very recent study revealed that CQ, in combination with remdesivir, is highly efficient in the management of COVID-19 infection in vitro. The authors therefore suggested that this drug combination should be further explored in patients suffering from COVID-19. Hence, CQ may be one of the best and cheapest medications to treat and prevent CoV infections.11

In a study on in vitro antiviral activity of hydroxychloroquine (HCQ) for the management of SARS-CoV-2, the authors demonstrated that hydroxychloroquine could be more potent than chloroquine to inhibit SARS-CoV-2 in vitro.12

### 2.2 | Steroids

Steroids were largely used in the outbreaks of SARS-CoV13 and Middle East respiratory syndrome (MERS)-CoV,14 and they have been used in patients with SARS-CoV-2 as well.15 Acute respiratory distress syndrome (ARDS) is the main cause of death in COVID-19. Pathophysiology of COVID-19 shows that a release of large amount of proinflammatory cytokines and chemokines occurs in patients with severe disease. Although steroid treatment may have a role in suppressing the lung inflammation and improve the patients’ situation, a meta-analysis of steroid use in patients with SARS indicated harm, and the current recommendation of WHO is against using steroids for management of severe acute respiratory infection in patients with COVID-19 unless indicated for another reason.16

| Drug | Route of administration | Potential advantage for COVID-19 | Potential reason for contraindication for COVID-19 |
|------|-------------------------|---------------------------------|-----------------------------------------------|
| Chloroquine and hydroxychloroquine | P.O. | • ACE2 downregulation  
• Immunosuppression  
• Inhibition of virus replication | None known |
| Systemic steroids | P.O./I.V. | • Inhibition of immunopathology, potentially useful with respiratory distress | Immunosuppressive in higher doses and on longer courses  
• Risk of opportunistic infections |
| MTX | P.O./S.C. | • None known | Immunosuppressive  
• Risk of opportunistic infections  
• Risk of eosinophilic pneumonitis |
| Cyclosporine A | P.O./I.V. | • Inhibits viral replication | Immunosuppressive  
• Risk of opportunistic infections |
| DMF | P.O. | • None known | Potential worsening of lymphopenia |
| PTX | P.O. | • Anti-inflammatory  
○ Antiviral  
○ Immunosuppressive  
○ Bronchodilator | None known |
| Doxycycline | P.O. | • None known | Decreased interferon type I  
• Increased viral replication |
| Azithromycin | P.O. | • Antiviral | None known |
| Ivermectin | P.O. | • Antiviral | None known |
| Dupilumab | S.C. | • ACE2 downregulation | None known |
| TNF-alpha antagonists | S.C. | • Interruption of the virus-induced inflammatory cascade  
• Reduction of disease severity and lung damage | Inhibition of innate anti-viral defense mechanisms |
| IL-12/23 inhibitors | S.C. | • None known | None known |
| IL-23 inhibitors | S.C. | • None known | None known |
| IL-17 inhibitors | S.C. | • None known | None known |
| Imatinib | P.O. | • Inhibits potential target of SARS-CoV | None known |

2.3 | Methotrexate

Acute psoriasis flares following respiratory virus infections caused by various CoV types, such as CoV-HKU1, CoV-OC43, and CoV-229, have been reported. This complication may require systemic therapy with immunosuppressive potential, including methotrexate (MTX). MTX treatment, however, may be associated with specific MTX-induced pneumonitis (MIP), which occasionally evolves to pulmonary fibrosis with a subsequent increase in mortality rate.17 MTX should therefore be avoided or only used with caution in patients with respiratory distress symptoms due to viral infections, especially CoV.
2.4 | Cyclosporine A

Calcineurin inhibitor cyclosporine A has the capability to block the replication of CoV of all genera.\(^{18,19}\) However, its potential clinical application as anti-CoV therapeutic remains limited by its immunosuppressive effects.\(^{20,21}\)

2.5 | Pentoxifylline

Pentoxifylline (PTX) has a tumor necrosis factor (TNF)-antagonizing and antiproliferative effect, hence used successfully in the treatment of psoriasis. It is a beneficent alternative therapy for pulmonary symptoms in patients with steroid-dependent sarcoidosis. Both psoriasis and sarcoidosis are more frequent in patients with ACE polymorphism.\(^{22}\) Being an anti-inflammatory, antiviral, immunomodulatory, and bronchodilator compound, PTX has been considered a promising drug in SARS treatment, alone or as adjuvant therapy with other medications.\(^{23}\) Due to its broad effects, we propose that PTX could theoretically be effective against COVID-19 as well.

2.6 | Tetracyclines and doxycycline

This group of medications is mostly used in inflammatory skin diseases including acne vulgaris. Doxycycline (DOX) has been found to increase intracellular levels of mitochondrial-specific reactive oxygen species (ROS) in a dose-dependent manner and to decrease production of interferon-\(\beta\). It has anti-inflammatory effects with inhibitory action on metalloproteases and modulating effects of proinflammatory cytokines including IL-6, IL-8, and TNF\(\alpha\) that have a major role in SARS-CoV-2 inflammation.\(^{24}\) Although DOX could promote COVID-19, clinical studies confirming this risk are still missing.\(^{25}\) Sodhi and his colleague stated that tetracycline due to its highly lipophilic characteristics chelates zinc compounds on matrix metalloproteinases (MMPs). Coronaviruses need MMPs for survival, cell-to-cell adhesion, cell infiltration, and replication, many of which have zinc as part of their MMP complex.\(^{26}\)

2.7 | Azithromycin

Azithromycin is well established as a potent treatment for skin infections and acne vulgaris. Azithromycin has been shown to be active in vitro against Zika and Ebola viruses.\(^{27,28}\) In a recent study, combination of hydroxychloroquine and azithromycin was effective in the early reduction of COVID-19 contagiousness.\(^{29}\)

2.8 | Ivermectin

Ivermectin is an antiparasitic medication that has become popular for treatment of scabies.\(^{30}\) It has been shown that ivermectin has broad-spectrum antiviral activity in vitro, and in their study Caly and colleagues stated that it is an inhibitor of the SARS-CoV-2 as well.\(^{31}\) Patri and colleagues hypothesized that combination therapy with HCQ and ivermectin may show a consequential and synergistic action in the treatment of COVID-19.\(^{32}\)

2.9 | Dapsone

Dapsone is an aniline derivative and is the first choice of treatment in chronic inflammatory dermatoses. It is effective in blocking inflammatory storms and, therefore, may be a promising therapeutic option of severe COVID-19 cases.\(^{33}\)

2.10 | Biologics

Lebwohl and colleagues stated that although there is no proven data whether biologics increase the susceptibility of the patients to coronavirus, in a pre-coronavirus state, the rate of respiratory infection was comparable to placebo (Table 2). In addition, we may increase the risk of loss of response if we discontinue biologics when they are reintroduced to the patients.\(^{34}\)

2.11 | Dupilumab

A previous study showed that the risk of severe viral pneumonia, including CoV infection, increased by 2.4 times in patients with a history of eczema, leading to the conclusion that major attention should be paid to infected patients with atopy.\(^{35}\) Dupilumab is a novel therapeutic option for patients with moderate-to-severe atopic dermatitis. It blocks IL-4/IL13-signaling and thereby inhibits receptor signaling downstream the JAK-STAT pathway. Interestingly, IL-4 and IL-13 can increase the ACE2 receptor in primary human alveolar type II cells.\(^{36}\) Thus, patients with atopic dermatitis treated with dupilumab and exposed to COVID-19 could find this drug as a protective medication. On the other hand, any drug with target immune mechanisms could be found to have the opposite effect. Patients with eczema being treated with dupilumab should be carefully studied for both positive and negative effects of COVID-19.

2.12 | Other biologics

Increased stimulated TNF\(\alpha\) secretion with increasing age has been demonstrated as a possible explanation for the age-related severity of illness in SARS. TNF\(\alpha\) inhibition was thought to have the potential to dramatically reduce disease severity and lung damage through interruption of the virus-induced inflammatory cascade, without interfering with the viral clearance. Researchers favored etanercept as the first choice anti-TNF\(\alpha\), owing to its long record of safety, reduced immunogenicity, and short half-life. However, a potentially great disadvantage of TNF\(\alpha\) inhibitors might be their inhibition of innate antiviral defense mechanisms.\(^{37}\)
Increased expression of numerous cytokines, containing IL-12/23p40, within the brain following either lethal or nonlethal CoV-induced acute encephalomyelitis, indicates that IL-12 expression may affect the generation of interferon (IFN) gamma-secreting T cells. However, therapeutic strategies designed to inhibit IL-12 and/or IL-23 failed to show significant impairment of the generation of functional virus-specific T cells. Proinflammatory cytokines related to the IL-17 pathways have been reported to be induced by respiratory viruses such as SARS-CoV. Whether modulation of the IL-17 inflammatory pathway or IL-17A-related gene expression might be a potential treatment option for other CoV types such as SARS-CoV-2 is still a matter for further research.

### IMMUNOTHERAPY MEDICATIONS

#### 3.1 Imatinib

Imatinib is used in dermatology for the treatment of various skin diseases, for example, dermatofibrosarcoma protuberans, melanoma, mastocytosis, and graft-vs-host disease. It has been stated that the imatinib target, Abelson tyrosine-protein kinase 2 (Abi2), is needed for efficient SARS-CoV and MERS-CoV replication. Imatinib could theoretically be effective against COVID-19. No clinical evidence of effectiveness has been published.

### CONCLUSION

In the setting of a catastrophic viral pandemic, a careful examination of the dermatology toolbox is in order. In our opinion, it might be prudent to wait until after the threat of COVID-19 diminishes before starting new immunosuppressive drugs such as prednisone, MTX and cyclosporine. Patients currently taking biologic immunomodulatory medications are by definition in a risk group and must avoid infection by social distancing and all other suitable measures. Further studies are required to determine whether established drugs commonly utilized in dermatology could be repurposed to thwart further spread of the COVID-19 pandemic through use of novel treatment strategies.

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