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# Systemic Medications of Dermatological Importance in COVID-19

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## ABSTRACT

Early December 2019 witnessed an international outbreak of a novel coronavirus (COVID 19) designated severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2). Since then, a number of therapeutic molecules have been explored to have potential efficacy against the SARS-Cov-2 per se or its sequelae. There are no Food and Drug Administration specific therapies approved so far; however, numerous drugs based on varying levels of evidence, in vitro studies and compassionate drug trials are being established as therapeutic agents, especially drugs approved for previous emergence of the severe acute respiratory syndrome (SARS-CoV-1) and Middle east respiratory syndrome coronavirus (MERS-Cov). Numerous active clinical trials for COVID-19 with more than 150 drugs and products are under study. Needless to say, many dermatological drugs are being employed to mitigate this pandemic threat. We aim to review drugs with potential against SARS-Cov-2 widely used in dermatology practice. Additionally, rampant and overzealous use of these drugs as well as introduction of new molecules might lead to emergence of adverse effects associated with these agents. Dermatologists must be on lookout for any cutaneous adverse effects of these drugs.

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## INTRODUCTION

In light of the severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) infection being declared a pandemic by World Health Organization (WHO), the International Clinical Trials Registry Platform of WHO has recorded more than 1000 clinical trials to study and develop therapies for the COVID-19 infection.[1-3] The Solidarity Trial by WHO aims to reduce the time taken for clinical trial by 80% and includes four treatment options (remdesivir, lopinavir/ritonavir, lopinavir/ritonavir with interferon beta-1a and chloroquine or hydroxychloroquine) against standard care, to assess effectiveness against COVID-19.[4] Additionally, numerous clinical trials, including drugs used in dermatology, are under study against SARS-Cov-2 infection. We highlight these dermatological drugs and review the adverse effects associated with other drugs being studied.[5-8]

### Dermatological drugs with efficacy against SARS-Cov-2

*Antimalarials*

In view of clinical studies and their in vitro effects, hydroxychloroquine (HCQ) and chloroquine (CQ) have been recommended as prophylactic agents in COVID-19 and included in the (HCQ) Chinese guidelines for COVID-19 management. The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to allow the emergency use of HCQ.[9] These antimalarials possess antiviral activity owing to inhibition of viral entry into the cell via pH dependant endocytosis, inhibition of glycosyl-transferases, and viral post-translational modifications. Wang et al[10] proved in vitro suppression of viral infection at both entry and at post-entry stages of the 2019-nCoV infection in Vero E6 cells by CQ in combination with remdesivir. CQ might have additional antiviral action by inhibition of quinone reductase-2, an enzyme involved in sialic acid biosynthesis, as sialic acid is present on SARS angiotensin-converting enzyme 2 receptors.[11] These also have immunomodulatory functions by guarding against the cytokine storm associated with disease severity of SARS-CoV-2. HCQ was shown to be a more potent agent than chloroquine in inhibiting SARS-CoV-2 in vitro.[12] HCQ successfully lead to negative viral RNA in nasopharyngeal samples after 6 days. Viral clearance was seen in 12.5% of patients who did not receive HCQ, in 70% of those treated with HCQ alone, and in 100% of those treated with HCQ combined with azithromycin.[13]

HCQ has been associated with severe cutaneous adverse drug reaction (generalized pustular figurate erythema, toxic epidermal

necrolysis (TEN), exfoliative dermatitis, erythroderma, erythema multiforme (EM), erythema annulare centrifugum, lichenoid eruptions, phototoxicity, blue-grey nail and mucosal pigmentation, and alopecia.[14,15]

**Antivirals**

*Lopinavir/Ritonavir*

An antiretroviral protease inhibitor with Lopinavir boosted by Ritonavir in a fixed drug combination has shown in vitro inhibitory action on SARS-Cov-2 by binding to the active site of SARS-CoV 3C-like protease (SARS-CoV $3CL^{pro}$).[16] However, Cao et al has shed a doubtful benefit of this therapy when compared to standard care.[17]

The known cutaneous side effects of Lopinavir/Ritonavir include eczemas, acne, stomatitis, alopecia, maculopapular rash, exfoliative dermatitis, and acute generalized exanthematous pustular (AGEP).[18,19]

**Glucocorticoids**

Uncontrolled immunologic response to the virus leads to a pro-inflammatory cytokine storm and inflammation, which are responsible for fatality associated with severe pneumonia caused by infection with COVID-19. Glucocorticoids are employed to manage this infection due to their anti-inflammatory role, as was previously done with SARS and MERS viruses.[20] However, corticosteroids delayed viral clearance and increased rates of secondary infections. The World Health Organization has recommended against routine use of systemic glucocorticoids in COVID-19 patients.[21] However, the Chinese Thoracic Society in a consensus statement has recommended using corticosteroids in pneumonia associated with COVID-19.[22]

A number of cutaneous adverse effects are secondary to use of corticosteroids, including acne, hypertrichosis, telangiectasia, candidiasis, poor wound healing, seborrheic dermatitis, striae, and AGEP.

**Ivermectin**

Oral ivermectin, an anti-parasitic drug, has shown to have broad-spectrum anti-viral activity in vitro. Caly et al have reported successful inhibition of SARS-CoV-2 with a ~5000-fold decrease in viral RNA at 48 hours utilizing a single treatment of viral cell culture.[23] The addition of ivermectin to HCQ has been hypothesised to have a synergistic role in chemoprophylaxis and treatment of COVID-19.[24] Oral ivermectin is widely and safely employed in mass treatment programs in Africa for onchoceriasis.[25] Generalized pruritus has been reported following ivermectin intake.

**Azithromycin**

Azithromycin, a macrolide antibiotic used in uncomplicated skin and soft tissue infections, has shown in vitro activity against Zika and Ebola viruses and in the prevention of severe respiratory tract involvement in viral infections, probably owing to its immunomodulatory action. Antiviral action of HCQ against COVID-19 was shown to be reinforced by azithromycin with a synergistic action.[13,26]

Cutaneous side effects are uncommon, but include EM, urticaria, angioedema, fixed drug eruption, vasculitis, photosensitivity, vasculitis and rarely SJS.[26]

**Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)**

There were emerging concerns related to the use of NSAIDs in COVID-19 infection, particularly with ibuprofen, with French authorities suggesting it as detrimental. Ibuprofen leads to increased expression of ACE2 in diabetics and those being treated with angiotensin II type-I receptor blockers, which could facilitate infection with COVID-19.[27] In vitro action of indomethacin possesses potent antiviral activity against canine coronavirus, thereby inhibiting virus replication.[28] The further role of NSAIDs in management of COVID-19 is yet to be explored.

Morbilliform rashes, SJS, EM, urticaria, angioedema, vasculitis, phototoxic drug reaction, aggravation of systemic lupus erythematous, and pemphigoid-like reactions are known to uncommonly occur with NSAIDs.

**Tetracyclines and Doxycycline**

Tetracycline, in addition to being antibacterial, has anti-inflammatory and immunomodulatory roles by scavenging intracellular reactive oxygen species, downregulating the NFKB pathway, and decreasing levels of inflammatory cytokines such as TNF-α, IL-1β, and IL-6. These cytokines are significantly elevated in COVID-19 infection, which could be downregulated by tetracyclines, including doxycycline. A potential therapeutic efficacy of tetracycline in treating COVID-19 has thus been hypothesised.[29]

Cutaneous side effects of tetracyclines are uncommon, but include maculopapular rashes, exfoliative drug rashes, onycholysis, photosensitivity, teeth and nail discoloration, urticaria, angioedema, exacerbation of systemic lupus erythematosus (SLE), serum sickness-like reaction, glossitis, black hairy tongue, and anogenital candidiasis.

**Thalidomide**

Thalidomide has anti-inflammatory, anti-fibrotic, anti-angiogenesis, and immune regulation effects. The safety and efficacy of thalidomide as a pulmonary anti-inflammatory and anti-fibrotic agent have been evident in idiopathic pulmonary fibrosis and severe H1N1 influenza lung injury. Its role to control or relieve lung inflammation is under study in clinical trials for COVID-19 therapy.

**TABLE 1.**

| Drugs Under Evaluation in SARS-Cov-2 Infection With Cutaneous Adverse Effects | | |
|---|---|---|
| **Drug** | **Proposed Mechanism against COVID-19 infection** | **Cutaneous adverse effect** |
| Remdesivir | Nucleoside analogue; Premature termination of RNA transcription | Not reported |
| Ribavarin | Nucleoside analogue; Use in hepatis-C infection | Pruritus, EM, Lichenoid drug eruptions, Fixed drug reactions, aggravation of rosacea, psoriasis, vitiligo, alopecia areata, sarcoidosis, herpes simplex reactivation |
| Favipiravir | Inhibition of RNA dependant RNA polymerase; Used in Influenza | Not reported |
| Interferon gamma | Immunomodulator | Injection site erythema/ tenderness, Maculopapular rash |
| Arbidol hydrochloride | Viral fusion inhibition with the targeted membrane blocking virus entry into the cell; Use in Influenza A and B | Not reported |
| Imatinib | Abelson tyrosine-protein kinase-2 inhibitors | Periorbital and facial oedema, Macupapuplar rash, Pruritus, Alopecia, Stomatis, Exfoliative drug rash, SCAR, Lichenoid drug rash |

Morbilliform to maculopapular rashes, seborrheic dermatitis, erythema nodosum, purpura, petechiae, exfoliative erythroderma, EM, TEN, and drug reaction with eosinophilia and systemic symptoms have been reported.[30]

**Drugs explored/ being studied in SARS-Cov-2 infection with cutaneous adverse effects**

Various drugs such as remdesivir, ribavirin, interferon gamma, favipavir, arbidol hydrochloride, imatinib are being studied for their potential activity against SARS-Cov-2 infection.[31] Table 1 highlights the probable mechanism of antiviral action and reported cutaneous adverse effect of these drugs.

## CONCLUSION

With current existing limited clinical evidence of the majority of drugs proposed against SARS-Cov-2, a number of therapeutic agents are being explored globally against this catastrophic viral pandemic.[32] Reinforcement of a few commonly utilized dermatological drugs with efficacy against this viral infection in mitigating active infection and its sequelae can further add to the novel treatment strategies. Dermatologist all across the world need to be aware of the potential adverse reactions of the known as well as these new drugs in light of their potentially overzealous use.

## DISCLOSURES

The authors have no conflict of interest to declare.

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