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SHORT PAPER

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Dermatological therapies with relevance to COVID-19

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel single-stranded RNA virus that has gripped humanity all over. It affects primarily the respiratory system, but is not limited to it, causing widespread involvement of many organ systems. The cases are still rising at an exponential rate and manifold trials are on to test different agents with the hope for potential limitation of spread and control of symptoms. Various classes of drugs have been tried; some with moderate success while many are yet to be proven to be of definite benefit. We have observed that the drugs used in dermatology practice are featured in more than a few of such studies. Here, we wish to highlight the ones that we are familiar with, which has featured at some point, in the management of this very challenging pandemic.

KEYWORDS

COVID-19, dermatological therapies, hydroxychloroquine, SARS-CoV-2

1 | INTRODUCTION

The end of 2019 witnessed the outbreak of the novel 120 nm coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) resulting in a mammoth epidemic throughout China, exponentially spreading to almost every continent except Antarctica. Rapidly evolving lines of treatment and hundreds of trials to salvage complications, and containing the spread of disease at the earliest, are ongoing.

Despite the fact that it is a condition affecting primarily the respiratory system, its therapeutic trials have witnessed many of dermatology drugs that are in use.

1.1 | Antimalarials

One of the earliest drugs to find widespread usage and give potential hope was hydroxychloroquine (HCQ), with its immunomodulatory mechanism showing effective inhibition of the entry, transport, and the postentry stages of SARS-CoV-2.[1] It was further shown to control the cytokine storm occurring late phase in critically ill SARS-CoV-2-infected patients.[2] Pasquale et al suggested the role of HCQ as a prophylactic agent for prevention of transmission, to those healthcare workers (HCW) exposed to the SARS-CoV-2.[3]

With reports suggesting that the addition of the macrolide antibiotic azithromycin as a possible therapeutic agent in coronavirus disease (COVID-19), a retrospective data among patients hospitalized in New York observed that treatment with HCQ, azithromycin, or a combination of both drugs, compared with neither treatment, was not significantly associated with differences in in-hospital mortality.[4]

Expressing concerns on the combination of azithromycin/HCQ on QT interval prolongation, Claudio et al suggested doxycycline (semi-synthetic derivative of tetracycline) as a safe and inexpensive alternative agent to azithromycin. Doxycycline is known to have anti-inflammatory effects at both low and high doses, ranging from 20 mg/day up to 200 mg/day, by inhibiting metalloproteases and modulating the effects of pro-inflammatory cytokines (interleukin-6 [IL-6], IL-8, and tumor necrosis factor alpha (TNFα).[5]

With all of the initial attention on HCQ, it was observed that patients were irrationally scrambling to increase their HCQ stock fearing shortage of drug supply.[6] Conclusive study results for HCQ, however, have been lacking. In a letter to the *Lancet*, the authors expressed apprehension in case of its widespread and indiscriminate usage as potentially contentious.[7]

1.2 | Anthelmintics

Another interesting agent is ivermectin, a Food and Drugs Administration-approved broad-spectrum antiparasitic agent, which was shown to inhibit SARS-CoV-2 virus in vitro, with ~5000-fold reduction in virion activity at 48 hours in cell culture.[8] Ivermectin has previously been shown to be an inhibitor of interaction between different RNA viruses and the human immunodeficiency virus-1 (HIV-1) integrase protein (IN) and importin (IMP)α/β1 heterodimer responsible for IN nuclear import of viral proteins. Its broad-spectrum antiviral activity is thought to be by sequestering IMPα/β1 on the rough endoplasmic reticulum/Golgi membrane. Translating the impact of ivermectin's effect on nuclear transport inhibitory activity in vitro, the authors have suggested a trial of ivermectin as an antiviral agent against SARS-CoV-2.

1.3 | Immunosuppressive agents

From Wuhan, in a single center experience of 15 patients, the authors reported an efficacious response using a trial of tocilizumab, a monoclonal antibody, particularly in the subset with cytokine storm by inhibiting binding to IL-6 to its receptors.[9] Meanwhile, it is learned that angiotensin-converting enzyme 2 is a possible receptor for SARS-CoV-2. One of the mediators is AP2-associated protein kinase 1 (AAK1), which is a known inhibitor of baricitinib, thus proposed in patient management of COVID-19.[10]

1.4 | Intravenous immunoglobulin

Historical therapeutic evidence with the SARS and Middle East respiratory syndrome (MERS) experience showed that the main pathogenesis of organ dysfunction lies in cytokine dysregulation, wherein intravenous immunoglobulin (IVIg) therapy exhibited well-tolerated clinical benefits. Given the phylogenetic relation of MERS-CoV with SARS-CoV-2, IVIg given at high dose of 0.3 to 0.5 g per kg weight per day for 5 days was tried on three patients with severe COVID. Promising results were shown when used at an early stage of clinical deterioration. Its immunomodulatory mechanisms, including Fc-mediated and Fab-mediated approaches, have been credited for the response.[11]

1.5 | Corticosteroids

Of caution to be exercised is the use of corticosteroids. Given its propensity to depress immunity and worsen comorbidities such as insulin resistance, appropriate dosing at the right stage of intervention is advised, after weighing risk-benefit ratio. In a Chinese study assessing the outcomes among patients with acute respiratory distress syndrome (ARDS) and mortality, treatment with methylprednisolone proved beneficial with decreased risk of mortality, in those with ARDS.[12] However, Tang et al warned against the improper use of systemic corticosteroids due to the heightened risk of osteonecrosis of the femoral head.[13] Emphasis is to be made on keeping it only as a reserve drug for critical cases such as septic shock.

1.6 | Anti-retroviral agents

An New England Journal of Medicine study of protease inhibitors lopinavir-ritonavir showed no benefit and trial halted in 13% patients due to adverse effects.[14]

1.7 | Apremilast-phosphodiesterase-4 inhibitor

COVID-19 and the concurrent use of biologics in psoriasis have prompted fears onto treating dermatologists by virtue of sustained immunosuppression, putting patients as vulnerable groups for contracting infections. Quelling these fears, Yu et al suggest ongoing treatment with phosphodiesterase-4 inhibitor apremilast might, in fact, play a protective role against the evolution of the infection caused by decreased expression of TNFα.[15] A previous report on elderly psoriatic patients receiving secukinumab (anti-IL-17) and adalimumab (anti-TNFα) was promising, with patients being unreceptive to COVID-19.[16]

1.8 | Vitamin supplements

We also wish to highlight reports of a new randomized controlled trial of 140 patients to assess intravenous vitamin C for the treatment of severe 2019-nCoV-infected pneumonia in Wuhan, China. Based on previous trials in ARDS for its antioxidant properties, intravenous vitamin C is being administered at a dose of 24 g/day for 7 days.[17] Besides vitamin C, it has also been found that low average vitamin D levels in a country are associated with a relatively high number of COVID-19 cases and mortality. In light of this, vitamin D supplementation is expected to be proven beneficial and protect against SARS-CoV-2 infection.[18]

1.9 | Vaccines

Curtis et al highlighted the off-target effects of the BCG vaccine.[19] It has the potential to induce metabolic and epigenetic changes, enhancing the innate immune response to infections— "trained immunity." This can reduce viraemia in COVID-19 affected patients.

1.10 | Androgenic theory and role of antiandrogens

Wambier et al in their exploration of the COVID pathogenesis explain in their hypothesis why males seem to be more vulnerable reporting

higher mortality rates and attribute it to androgen receptor gene polymorphisms.[20]

Based on this, it was suggested that agents halting androgen activity, such as androgen receptor inhibitors, steroidogenesis inhibitors, and 5-alpha reductase inhibitors may play a role in therapeutics.

2 | CONCLUSION

Many potential drugs are being investigated in SARS-CoV-2 treatment for safety and efficacy. The race is on for vaccine development as that could be the potential game changer in how the infection is halted. However, in the absence of robust trials with conclusive evidence of antiviral efficacy, trials of different therapeutics based on pathogenesis and previous reports appear to be the majority approach.

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