COMMENTARY

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# SARS-CoV-2 virus infection: Targets and antiviral pharmacological strategies

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## 1 | INTRODUCTION

The current pandemic of coronavirus disease 2019 (COVID-19) poses a threat to global public health owing to its high rate of spread and its association with severe forms of respiratory infection, including pneumonia.[1–3] It is characterized by an exaggerated immune response (cytokine storm) with high TNF-$\alpha$ levels, among other cytokines. It has a high risk of mortality in the older population with cardiovascular (coronary artery disease, heart failure, and cardiac arrhythmias) and pulmonary (chronic obstructive pulmonary disease) comorbidities.[4]

COVID-19 is transmitted from person to person by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a single-stranded positive-sense RNA virus. The SARS-CoV-2 genome shows a 5′ untranslated region (UTR), replicase enzyme coding region, S gene, E gene, M gene, N gene, 3′ UTR, and several unidentified nonstructural open reading frames.[5]

This genome encodes four main structural proteins: spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins. The S protein is the receptor-binding site on the viral surface; the M protein shapes the virions, promotes membrane curvature, and is responsible for the transport of nutrients across cell membranes; the E protein plays a role in the assembly and release of the virus, and is involved in viral patho-

genesis; and the N protein can bind to the viral RNA genome and maintain its stability.[6,7]

The current pharmacological strategies against COVID-19 are based on improve the immune responses to SARS-CoV-2 and prevent its severe complications.[6] To date, there are no clinically approved antibodies or drugs specific for SARS-CoV-2, making the control of the associated pandemic difficult; therefore, health services are limited to monitoring and containment of the virus. This situation requires the development of safe and effective treatments, and investigation into the history of treatments for similar outbreaks is necessary to extrapolate potential antiviral therapies.[1–3]

SARS-CoV-2 shares phylogenetic traits with SARS-CoV and MERS-CoV; therefore, antiviral treatments effective against these viruses may provide some insight into the development of therapeutics for COVID-19. Due to the nature of the pandemic, priority is being given to FDA-approved drugs or clinical trial candidates in Phase III that are close to being commercialized.[1–3] Also, the immunotherapies may be effective in the early stages of infection. The use of convalescent plasma, intravenous immunoglobulin, and monoclonal antibodies can provide virus-neutralizing and inhibition effects. The lung damage of COVID-19 is, at least partially, mediated by the immune response against the virus, and it is theoretically possible that modulating that

inflammation by TNF-$\alpha$, IL-17, and IL-23 inhibition might even be protective.[4,8]

## 2 | SPIKE PROTEIN INHIBITORS

The molecular interaction of the virus with the host cell represents a promising therapeutic target for identifying SARS-CoV-2 antiviral drugs and is the main target of neutralizing antibodies (Abs) upon infection. The coronavirus enters the host cell via binding of S glycoprotein on the viral surface to angiotensin-converting enzyme 2 (ACE2) on the cell surface, which is triggered by transmembrane serine protease 2 (TMPRSS2). The S2 subunit of S glycoprotein is responsible for mediating virus fusion and entry into the host cell, where heptad repeat 1 (HR1) and 2 (HR2) bring viral and cellular membranes in proximity for fusion.[6,9] The binding affinity of the S protein-ACE2 complex of SARS-CoV-2 is approximately 10-20 times higher than that of SARS-CoV.

A high-throughput in silico screening approach used to investigate FDA-approved compounds in the LOPAC library identified KT185, KT203, GSK1838705A, BMS195614, and RS504393 (Eptifibatide acetate, TNP, GNF5, GR 127935 hydrochloride hydrate, and RS504393, respectively). These compounds were shown to interact with the receptor-binding site on the viral S protein (similar to the virus binding motifs of ACE2), and are therefore potential drugs for the inhibition of viral infection.[10] The lectin griffithsin is one of the most potent broad-spectrum antivirals, and viral entry inhibitors discovered to date.[11] This binds to the oligosaccharides of various viral surface glycoproteins, including those found on HIV, MERS, SARS, HCV, and HSV.[12] Griffithsin has been tested for HIV prevention in Phase I studies, but the potency and delivery systems of known S protein inhibitors should be reevaluated for the treatment or prevention of COVID-19.

## 3 | TMPRSS2 INHIBITORS

TMPRSS2 is a host protein that sits on the cell membrane and is considered a promising drug target. This serine protease is critical to the entry of coronaviruses into host cells by cleaving and activating the viral S protein, and viral entry has been blocked by a clinically proven inhibitor of TMPRSS2, imatinib.[1,13,14] From this perspective, it is believed that other serine protease inhibitors such as imatinib, camostat, and nafamostat can efficiently block SARS-CoV, MERS-CoV, and SARS-CoV-2 cell entry, which could be a promising treatment for COVID-19 infection.[14–16]

## 4 | MPRO INHIBITORS

The main protease (Mpro, also known as 3C-Like protease) of SARS-CoV-2 functions in the processing of polyproteins and virus maturation, cleaving nsp4-nsp16. The crucial role of Mpro in viral replication and its high sequence conservation with SARS-COV Mpro (96% homology) makes this enzyme a promising antiviral target.[1,17,18] Studies have adopted a computational approach to screen for available medicines which may function as inhibitors of SARS-CoV-2 Mpro.

Based on the chemical structures of the potential drugs and conformational changes in the active site, binding of SARS-CoV-2 Mpro occurs with the following compounds: colistin, valrubicin, icatibant, bepotastine, epirubicin, epoprostenol, vapreotide, aprepitant, caspofungin, and perphenazine.[19] In addition, similar studies have highlighted the compounds myristicin, methyl rosmarinate, calceolarioside B, licoleafol, amaranthine, nelfinavir, and prulifloxacin from a total of 32 297 potential antiviral phytochemicals,[20] and nelfinavir in combination with the inhibitor N3 showed potential for inhibition during in vitro studies.[1,17,21]

A previous attempt to predict drugs that inhibited SARS-CoV Mpro identified two HIV-1 protease inhibitors, lopinavir and ritonavir (LPV/r), as potential candidates, both of which bind to the same target site of Mpro.[22] These drugs were assessed for activity against SARS-CoV-2 using in silico studies, and administration of LPV/r to infected COVID-19 patients appeared to show therapeutic effect, lowering the body temperature and restoring standard physiological mechanisms with no apparent toxicity or side effects.[23]

However, LPV/r treatment did not result in benefits beyond standard therapy in severe cases of COVID-19, while a retrospective study found no protective effect of these drugs for the treatment of nonsevere COVID-19 patients.[24,25] In order to fully investigate the efficacy of LPV/r antiviral treatment, a Phase IV randomized controlled trial of LPV/r for COVID-19 treatment is being carried out (No.NCT04255017).

## 5 | NUCLEOSIDE ANALOGS (REMDESIVIR AND FAVIPIRAVIR)

Attention has shifted to remdesivir and favipiravir, drugs with a wide spectrum of action which possibly have the highest potential for the effective treatment of COVID-19. These drugs are nucleoside analogs that act as RNA-dependent RNA polymerase (RdRp) inhibitors, capable of interfering with the action of viral RNA replicase and avoiding proofreading by viral exoribonuclease (ExoN), inhibiting the replication of multiple coronaviruses in respiratory epithelial cells.[25,26]

Remdesivir is highly effective and safe in controlling COVID-19 infection. In SARS-CoV-2 infected Vero E6 and Huh-7 cells, remdesivir and favipiravir showed inhibition at micromolar concentrations.[26] A report was recently published describing the successful administration of remdesivir in the first case of COVID-19 in the United States when the clinical status of the patient worsened.[27] Attention should be focused on the pharmacokinetics of remdesivir and kinetics of COVID-19 in the ongoing Phase III clinical trials. Two randomized controlled clinical trials are in progress in China, evaluating the efficiency of remdesivir in severe and mild-moderate disease (NCT04257656 and NCT04252664, respectively). However, in the absence of these results, it is challenging to put remdesivir into large-scale clinical use.[28,29]

Although favipiravir showed a higher inhibitory concentration than remdesivir against SARS-CoV-2, favipiravir was shown to have 100% efficacy against the Ebola virus, which has a similar inhibitory concentration.[26] A study comparing favipiravir and LPV/r for the treatment of patients infected with COVID-19 reported that favipiravir resulted in a better therapeutic response in terms of disease progression and viral clearance.[30] In addition, favipiravir can inhibit the binding of the viral envelope and ORF7a proteins to porphyrin, preventing the virus from entering host cells and freeing porphyrins.[31]

## 6 | CHLOROQUINE AND HYDROXYCHLOROQUINE

The antimalarial chloroquine (CQ), along with its analogue hydroxychloroquine (HCQ), was officially declared as a medical agent for COVID-19 by the National Health and Care Commission of China in February and granted Emergency Use Authorization (EUA) by the FDA in March.[32,33] Recent bioinformatic analysis revealed that SARS-CoV-2 proteins might attack the heme on the $\beta$-1 chain of hemoglobin, causing the dissociation of iron to form a porphyrin, which would result in hypoxia. CQ may prevent this by preventing the binding of the viral proteins to hemoglobin, effectively relieving respiratory complications (such as pneumonia), which could be particularly beneficial for patients with comorbidities.[31]

HCQ-azithromycin combination therapy has been identified as a potential treatment, reported as the first repurposed drug showing excellent results in clinical trials against SARS-CoV-2.[34] Although in vitro studies suggested that HCQ is more effective and less toxic than CQ,[35,36] no evidence of antiviral activity or clinical benefit was found for HCQ-azithromycin combination therapy in patients with severe cases of COVID-19.[37] A study, led by a team from the Clinical Center for Public Health in Shanghai, China, demonstrated that HCQ monotherapy was not effective in treating patients hospitalized for COVID-19. However, only a small number of patients were included in the study; therefore, larger sample size is needed to comprehensively investigate the effects of HCQ in the treatment of COVID-19.[38]

The CQ/HCQ cardiac safety profile is being questioned due to their known cardiotoxic effects, including vasodilatation, hypotension, hypokalemia, negative inotropy, and arrhythmias. Using the QT interval as the marker for electrocardiographic safety, a small increase in QT associated with the use of chloroquine (not hydroxychloroquine) was observed in subjects free of COVID-19, and no increased mortality associated with the use of hydroxychloroquine.[39] In an observational study, the association between hydroxychloroquine use and intubation or death at a large medical center in New York city was examined. In case, HCQ administration was not associated with either a significantly lowered or an increased risk of the composite endpoint of intubation or death.[40] Even so, care and careful monitoring for cardiac arrhythmias are essential while using these drugs alone or in combination with azithromycin, especially in patients with comorbidities as cirrhosis, heart failure, or preexisting QT-prolongation.[41] Randomized, controlled trials of hydroxychloroquine in patients with COVID-19 are needed.

## 7 | NITAZOXANIDE AND IVERMECTIN

Studies of the antiparasitic agents nitazoxanide and ivermectin have reported broad-spectrum antiviral activity in vitro. Therefore, these drugs are being investigated in randomized controlled clinical trials for the management of acute respiratory infections, including COVID-19.[42]

Nitazoxanide is an active metabolite that has demonstrated potent activity against SARS-CoV-2 in vitro, yielding inhibitory concentrations in the micromolar range for infected Vero E6 cells.[26] It is believed that this activity is due to interference with pathways in the host involved in viral replication, rather than virus-specific pathways, where innate antiviral mechanisms are upregulated by amplification of cytoplasmic RNA sensing and type I IFN pathways.[42,43]

Ivermectin was found to inhibit SARS-CoV-2 in an in vitro study utilizing Vero/hSLAM cells 2 hours after viral infection. The results showed a 93% reduction in viral RNA present in the supernatant after 24 hours, and viral RNA was reduced by ∼5000-fold at 48 hours compared to control, demonstrating a loss of virtually all viral material. In addition, no further reduction in viral RNA was observed at 72 hours, and no toxicity was observed. It was suggested that ivermectin inhibits the importin $\alpha/\beta$1-mediated nuclear import of viral proteins (which has been shown for other RNA viruses), disrupting the immune evasion mechanism of the virus.[42,44]

## 8 | OTHER POTENTIAL TREATMENTS

Teicoplanin, an antibiotic used to treat staphylococcal infections, has been shown to inhibit the first stage of the MERS-CoV life cycle in human cells. This activity appears to be conserved against SARS-CoV-2 in vitro.[45]

Baricitinib, a selective JAK1 and JAK2 inhibitor, has been identified as a potential treatment for SARS-CoV-2 that targets host pathways. Stebbing et al[46] indicated that baricitinib could inhibit viral endocytosis in lung cells and, in combination with direct-acting antivirals, reduce viral infectivity, viral replication, and the aberrant host inflammatory response. However, despite the unusual effect of directly blocking the entry of the virus into cells, the JAK-STAT signalling blocked by baricitinib impairs the interferon-mediated antiviral response, with a potential effect of facilitating the progression of SARS-CoV-2 infection.[47]

The natural progression of the host antiviral response involves triggering IFN-$\alpha$ and IFN-$\beta$, which play critical roles in viral innate immunity. In clinical isolates of SARS-CoV, IFN-$\beta$ was 5-10 times more potent than IFN-$\alpha$ at reducing viral replication, even when it was associated with ribavirin. These findings suggest that IFN-$\beta$ may be relevant for COVID-19 treatment. Studies utilizing a drug-target, which assesses target information against 2938 FDA-approved or experimental drugs,

identified 135 drugs that were associated with the host interactome of human coronavirus infection. Among these molecules, network-predicted evidence and gene set enrichment analysis identified 16 drugs with the potential to be repurposed and three possible effective drug combinations: sirolimus and dactinomycin, toremifene and emodin, and mercaptopurine and melatonin.[48]

A recent study on more than 20 000 COVID-19 patients who received convalescent plasma therapy reported clinical improvements and a reduction in mortality after the transfusion of convalescent plasma. In spite the adverse effects associated with plasma transfusion, such as pathogen transmission and allergic transfusion reactions, more than 130 clinical trials are in progress across the world to gather stronger evidence that would warrant the use of plasma therapy.[49]

## 9 | TREATMENTS THAT ARE NOT RECOMMENDED

In general, the pharmacological treatment in nonhospital settings is not recommended, as well as for young, healthy patients with mild symptoms, and without comorbidities.[50] Through the clinical treatment of the COVID-19, it has been found that neuraminidase inhibitors (such as oseltamivir, peramivir, and zanamivir) are not sufficient, as this viral enzyme is not produced by coronaviruses. Drugs such as ganciclovir, acyclovir, and ribavirin and lopinavir/ritonavir are have also been shown to be ineffective for serious cases and are thus not recommended for clinical application in these patients.[28]

Although SARS-CoV-2 infection is associated with a cytokine storm triggered by overactivation of the immune system, the corticosteroids treatment was not initially recommended for viral pneumonia, only for patients with refractory shock or acute respiratory distress syndrome.[18,49–51] Currently, a systematic living review and network meta-analysis with data from eight randomized trials (7184 participants) made a strong recommendation for use of corticosteroids in severe and critical COVID-19 because there is a lower risk of death among people treated with systemic corticosteroids (moderate certainty evidence). On the other hand, it suggests not to use corticosteroids in the treatment of patients with nonsevere COVID-19 (weak or conditional recommendation based on insufficient certainty evidence), but should not be stopped for those who are already treated with systemic corticosteroids for other reasons as chronic autoimmune diseases.[52]

In addition, the management of patients with COVID-19 showed that an artificial liver blood purification system could quickly clear inflammation mediators to suppress cytokine storm, but the repair system may be delayed for excessive clarity.[53]

It has been reported that remdesivir with chloroquine or IFN-$\beta$ can inhibit SARS-CoV-2 replication in vivo and in vitro, which is better than that of lopinavir/ritonavir-IFN-$\beta$ against MERS-CoV. However, its effectiveness and safety still need to be verified in clinical trials.[54] Finally, it should be noted that therapeutic-intensity anticoagulation is not recommended in the management of COVID-19 in the absence of confirmation of venous thromboembolism.[52]

## 10 | CONCLUSIONS

Despite recent advances to control the current COVID-19 pandemic, challenges such as the rapid spread of the virus and socioeconomic cost of the outbreak remain, in part, exacerbated by the lack of effective therapeutic agents against SARS-CoV-2. Clinical trials are currently underway to identify possible therapies; first, the *in vivo* evaluation of FDA-approved drugs which have shown preliminary evidence of efficacy, such as CQ, HCQ, remdesivir, favipiravir, nitazoxanide, and ivermectin, which should be followed by the assessment of Mpro, S glycoprotein, and TMPRSS2 inhibitors. Although certain prospective agents listed in this letter are promising, definitive evidence regarding their effectiveness remains inconclusive, this can be confirmed by randomized, double-blind placebo-control clinical trials. Despite this, repurposing of existing drugs and the use of nonpharmacological therapies such as convalescent plasma are currently the best treatment avenues until a safe and efficacious vaccine is discovered.

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