Commentary

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Update: Drug treatment options for coronavirus disease 2019 (COVID-19)

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SUMMARY Coronavirus disease 19 (COVID-19) continues to rage as a global pandemic. A number of potential therapeutic agents have been explored over the past year or two. However, numerous drugs that were expected to prove highly effective, such as lopinavir/ritonavir and remdesivir, have been found to have little benefit in large clinical trials. Interleukin-6 receptor antagonists, glucocorticoids, Janus kinase inhibitors, and some antivirals have been found to provide significant benefits in terms of reducing viral load, reducing the time of nucleic acid conversion, or improving survival. For example, bamlanivimab and etesevimab, which are newly designed monoclonal antibodies against the surface spike protein S1 subunit receptor-binding domain (RBD) of SARS-CoV-2, have a significant effect on reducing the viral load and the hospitalization rate of patients with mild COVID-19. Several vaccines against SARS-CoV-2 have been widely administered worldwide and have provided good protection. Nevertheless, the increasingly hardy variants of the virus have raised the requirements for vaccine design. Perhaps RBD-based vaccines are a viable way to defend against variants, but this still needs to be verified in a large sample. Therefore, this paper provides an update on the treatment options for COVID-19 based on three previously proposed dimensions of drug screening: standard assays of existing broad-spectrum antivirals, screening of chemical libraries, and redevelopment of new, specific drugs.

Keywords COVID-19, SARS-CoV-2, coronaviruses, drug therapy

As of August 14, 2021, there were 205 million cumulative diagnoses of coronavirus disease 19 (COVID-19) and 4.3 million deaths worldwide (*1*). The COVID-19 pandemic has triggered a global health crisis, and effective pharmacological interventions may be the solution to the existing dilemma. The current authors previously proposed three approaches to drug screening for the treatment of COVID-19 (*2*), and the current article updates the potential treatment options that are currently available (Table 1).

The first approach is to standardize existing broad-spectrum antivirals that are used to treat other viral infections. Representative drugs are interferon (INF) and ribavirin. *In vitro* experiments have confirmed that IFN-β effectively blocks the replication of SARS-CoV-2 (*3*). In a prospective, open-label, randomized, phase II trial in Hong Kong, 86 patients with COVID-19 were given subcutaneous INF β-1b along with lopinavir/ritonavir and ribavirin within 7 days of symptom onset for 14 days. The time to nucleic acid conversion (7 days verse 12 days) was significantly shorter in patients receiving the triple combination compared to the antiviral control group not receiving interferon (*4*). In the United Kingdom, a randomized, double-blind, placebo-controlled phase II trial that evaluated the effect of IFN β-1a, known as SNG001, after 14 days of continuous inhalation found a greater likelihood of improvement in patients receiving IFN β-1a than in the placebo group (*5*). However, another clinical trial of IFN beta-1a given subcutaneously or intravenously found that it did not reduce overall or subgroup mortality in patients with COVID-19 (*6*). Therefore, further clinical trials of IFN-β are urgently warranted.

The second method is to screen established chemical libraries and to then conduct antiviral trials.

Repurposing of older drugs has accelerated the deployment of new therapies for COVID-19. Based on previous experience with the treatment of SARS, Middle East respiratory syndrome, and other novel influenza viruses, numerous large-scale clinical trials have explored various drugs. Two studies have found that mortality and the need for invasive mechanical ventilation are reduced

Table 1. Potential COVID-19 drugs mentioned in this article

Drug therapy	Classification	Outcomes	Country/Research team	Ref.
INF β-1b +lopinavir/ritonavir +ribavirin	Broad-spectrum antiviral	Less time to nucleic acid conversion compared to that in the control group not receiving IFN.	China	(*4*)
IFN β-1a (SNG001)	Broad-spectrum antiviral	Patients who received SNG001 had greater odds of improvement and recovered more rapidly from SARS-CoV-2 infection.	The United Kingdom	(*5*)
Tocilizumab	Interleukin-6 receptor antagonist	Reduction in mortality and the need for invasive mechanical ventilation and improvement of outcomes, including survival.	RECOVERY Collaborative Group, REMAP-CAP Investigators, Netherlands	(*7-9*)
Sarilumab	Interleukin-6 receptor antagonist	Improvement of outcomes, including survival.	REMAP-CAP Investigators	(*8*)
Dexamethasone	Glucocorticoid	The 28-day mortality among those who were receiving respiratory support was lower.	RECOVERY Collaborative Group, COALITION COVID-19 Brazil III Investigators, Egypt	(*10-12*)
Nitazoxanide	Anti-parasite drug	Can induce a greater reduction in viral load.	SARITA-2 investigators	(*15*)
Molnupiravir	Nucleoside analogue	Highly effective at reducing nasopharyngeal SARS-CoV-2 and viral RNA.	United States	(*20*)
Imatinib	Tyrosine kinase inhibitor	May have a clinical benefit in terms of survival and the duration of mechanical ventilation.	Netherlands	(*21*)
Baricitinib	Janus kinase inhibitor	Baricitinib plus remdesivir was superior to remdesivir alone in reducing recovery time and accelerating improvement in clinical status.	ACTT-2 Study Group Members	(*22*)
Tofacitinib	Janus kinase inhibitor	Led to a lower risk of death or respiratory failure through day 28.	STOP-COVID Trial Investigators	(*23*)
Bamlanivimab +etesevimab	RBD monoclonal antibodies	Led to a lower incidence of hospitalization and death and accelerated the decline in the SARS-CoV-2 viral load.	BLAZE-1 Investigators, BLAZE-2 Investigators	(*25-26*)
REGN-COV2 (casirivimab +imdevimab)	RBD monoclonal antibodies	Reduced viral load.	Trial Investigators	(*28*)
Meplazumab	CD147 monoclonal antibody	Reduced the time to discharge, case severity, and the time to a negative test result.	China	(*30*)
CoronaVac	Inactivated vaccine	Effective in preventing COVID-19, including severe illness and death	Sinovac Research and Development Co., Ltd.	(*36*)
I-R-F vaccine (V-01)	Protein subunit	All vaccinated adults were positive for antibodies to the RBD after two doses	China	(*38*)

in patients receiving interleukin-6 receptor antagonists (*e.g.*, tocilizumab and sarilumab); the duration of mechanical ventilation and hospitalization may also be reduced (*7-9*). Similarly, a benefit from dexamethasone was also noted (*10-12*). The previous Solidarity trial, a global study led by the World Health Organization, found that remdesivir, hydroxychloroquine, and lopinavir had little or no effect on hospitalized patients with COVID-19, as evinced by overall mortality, initiation of ventilation, and duration of hospitalization (*6*). A study then analyzed a drug library of approximately 12,000 clinical-stage or Food and Drug Administration (FDA)-approved small molecules, and it identified 13 drugs, including kinase inhibitors and protease inhibitors, that were effective at concentrations commensurate with therapeutic doses (*13*). In addition, masitinib was found to influence SARS-CoV-2 replication by competitively inhibiting proteinase 3CL. Masitinib substantially inhibited several variants of concern such as B.1.1.7, B.1.351, and P.1. Animal studies indicated that the SARS-CoV-2 viral load in the lungs and nasal turbines of mice treated with masitinib decreased by more than 99% on day 6, and the extent of pulmonary pathology and levels of cytokines were significantly lower than those in the control group (*14*). More importantly, survival rates were also significantly higher in the treated group than in the control group.

In a multicenter, randomized, double-blind, placebo-controlled trial, the efficacy of nitazoxanide, an anti-parasite drug, was tested in 392 patients with COVID-19 who were hospitalized with adult-onset disease. Viral load decreased after 5 days of nitazoxanide treatment compared to a placebo (55% *vs*. 45%). However, there were no significant differences in the time to remission of symptoms (*15*). Another oral antiviral targeting mild COVID-19, molnupiravir, has been found to exhibit antiviral action in *in vitro* experiments primarily by increasing the rate of viral genomic RNA mutations

(*16,17*). Animal testing trials have also found it to be effective in reducing viral load (*18,19*). Results from a Phase IIa trial indicated a shorter time to viral RNA clearance and a greater proportion of participants achieving overall clearance with 800 mg of molnupiravir compared to a placebo (*20*). Molnupilavir was generally well tolerated, with a similar number of adverse events in all groups.

Tyrosine kinase inhibitor imatinib may reverse pulmonary capillary leak. A randomized, double-blind, placebo-controlled clinical trial was conducted in 400 hospitalized patients with COVID-19 who required supplemental oxygen to maintain a peripheral oxygen saturation greater than 94% (*21*). Imatinib did not reduce the time for discontinuation of ventilation and supplemental oxygen for more than 48 consecutive hours compared to a placebo. The observed effects on survival and the median duration of mechanical ventilation suggest that imatinib may provide a clinical benefit to patients hospitalized with COVID-19, and the Solidarity trial will confirm or reject these findings.

In addition, baricitinib, a selective Janus kinase 1 and 2 inhibitor for the treatment of rheumatoid arthritis, has been noted to have two major advantages in the treatment of COVID-19: possible anti-inflammatory and antiviral action. A randomized double-blind placebo-controlled trial noted a reduced mortality rate in patients requiring oxygen support who received baricitinib plus remdesivir compared to remdesivir alone (5.1% *vs*. 7.8%) (*22*). Another selective Janus kinase 1 and 3 inhibitor, tofacitinib, was associated with a lower risk of death or respiratory failure through day 28 than a placebo after treatment of 19 adult patients hospitalized with COVID-19 (*23*).

This strategy continues to offer promising and could be used to explore more drugs.

The third strategy is to directly target SARS-CoV-2 by designing and developing new drugs that target its genomic or biophysical structures. SARS-CoV-2 infects cells by binding to the angiotensin-converting enzyme 2 (ACE2) receptor on host cells *via* the surface spike protein and by inducing membrane fusion (*24*). Therefore, monoclonal antibodies and vaccines targeting the spike protein could be a way to treat and prevent COVID-19.

Bamlanivimab and etesevimab are monoclonal antibodies against the surface spike protein S1 subunit receptor-binding domain (RBD) of SARS-CoV-2. The antibodies were respectively isolated from the plasma of recovering patients with COVID-19 in the United States and China. A phase III trial involving 1,035 outpatients with COVID-19 of mild or moderate severity indicated that the combination of bamlanivimab and etesevimab (2,800 mg of bamlanivimab and 2,800 mg of etesevimab) reduced the incidence of hospitalization and death associated with COVID-19 compared to a placebo (2.1% *vs*. 7%) and accelerated the decline in viral load (*25*). This demonstrates the effectiveness of early administration of bamlanivimab plus etesevimab in reducing hospitalization rates. A point worth mentioning is that a previous randomized phase 2/3 trial, also in outpatients, noted a significant decrease in viral load between a combination of the two antibodies and a placebo, while there were no significant differences in viral load with bamlanivimab monotherapy, regardless of the dose (*26*). Studies in hospitalized patients have also found that bamlanivimab did not display efficacy even when combined with remdesivir (*27*). This may be because combining several types of antibodies helps to reduce the frequency of evasion of antibody-mediated neutralization due to viral variants.

REGN-COV2 is a combination of two powerful neutralizing antibodies, casirivimab and imdevimab, that bind to two distinct and non-overlapping sites on the RBD. An ongoing phase I study has indicated that REGN-COV2 enhanced viral clearance in outpatients with COVID-19, and particularly in patients who had not initiated an endogenous immune response (*i.e.*, serum antibody-negative) or who had a high baseline viral load, and it noted no serious adverse events in the high-dose group (REGN-COV2 8 g) (*28*).

In addition to the ACE2 receptor, direct interaction between CD147 and the SARS-CoV-2 spike protein can mediate viral infection of host cells (*29*). CD147 is a transmembrane glycoprotein of the immunoglobulin superfamily and is involved in several pathogenic processes such as tumor development and parasitic, bacterial, and viral infections. Therefore, meplazumab may, as a CD147 monoclonal antibody, be a new therapeutic pathway by inhibiting novel coronavirus replication through depletion of CD147 or blocking of CD147. Phase I and exploratory phase II clinical trials of meplazumab have been completed with favorable results in terms of safety and efficacy (*30*).

A vaccine to prevent SARS-CoV-2 infection is believed to be the most promising method to control the outbreak. Primate studies and human epidemiological studies have found that a SARS-CoV-2 infection causes the body to produce functional neutralizing antibodies that are protective against reinfection (*31-34*). Therefore, vaccines that elicit an adequate neutralizing response should protect against COVID-19. As of August 16, 2021, dozens of vaccines are available in different regions of the world, more than 100 vaccines are in clinical trials, and more than 180 vaccines are in preclinical trials (*35*). SARS-CoV-2 vaccine development has used a variety of different platforms, including conventional inactivated live inactivated vaccines (LIVs), live attenuated vaccines (LAVs), novel recombinant protein vaccines (RPVs), viral vector vaccines (VVVs), DNA vaccines, and RNA vaccines. Of the eight vaccines in Phase 4 clinical trials, three are non-replicating vector vaccines (ChAdOx1 nCoV-19/AZD1222, Ad26.COV2.S, Ad5-COVID-19), three are RNA vaccines (BNT162b2,

mRNA 1273, mRNA 1273.351), and the remaining two are inactivated vaccines (BBIBP-CorV, CoronaVac). After a SARS-CoV-2 vaccine becomes available and widely used, unresolved efficacy issues need to continue to be assessed in clinical trials and vaccine safety needs to be monitor. Data from mass vaccination with CoronaVac in Chile indicated that the vaccine was effective in preventing COVID-19, including severe illness and death (*36*). At the same time, the continued emergence of new variants poses a challenge for vaccine design and development, which is a fact that cannot be overlooked.

In vitro experiments recently indicated that a neutralizing antibody (named S2X259), broadly neutralizes multiple SARS-CoV-2 variants of concern (VOC), including B.1.1.7, B.1.351, P.1, and B.1.427/B.1.429 (*37*). This identification of monoclonal antibodies from memory B cells of individuals with COVID-19 who recovered may guide future efforts to develop novel vaccines that can overcome the emergence of variants.

Moreover, a randomized, placebo-controlled phase I/II trial of a human I-R-F vaccine (V-01) in 180 healthy adults has concluded. Developed in China, the vaccine was created by fusing IFN-α at the N-terminal end of the RBD after the RBDs were combined to immunoglobulin Fcs as a stable dimer. This structure increases the passage of vaccine molecules through the lymph nodes while improving the efficiency of dendritic cells in capturing and presenting antigens. Clinical trials have noted no serious adverse events and all vaccinated adults were positive for antibodies to the RBD after two doses of the V-01 vaccine (*38*). Because of its efficacy and safety, this engineered vaccine may be a next-generation candidate in the global effort to defeat COVID-19.

As new drugs are developed, combinations of neutralizing antibodies such as bamlanivimab plus etesevimab have superior efficacy and could potentially be potent agents, but further clinical trials still need to be conducted. The Solidarity clinical trial will test three new drugs in hospitalized patients with COVID-19: the anticancer drug imatinib, an antibody called infliximab for autoimmune diseases, and artesunate, an antimalarial drug (*39*). Several vaccines are now widely administered worldwide and provide good protection, but the emerging variants of SARS-CoV-2 are a serious challenge to be faced in vaccine design and development.

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