A narrative review of emerging therapeutics for COVID-19

Running title: Emerging therapeutics in COVID-19

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The novel coronavirus SARS-CoV-2, causal agent of COVID-19, quickly spread around the world resulting in the most aggressive pandemic experienced in over 100 years. Research into targeted therapies and vaccines has been initiated on an unprecedented scale and speed but will take months and even years to come to fruition. Meanwhile, the efficacy of emerging therapeutics for use in treating COVID-19 is feverishly being investigated to identify the best available treatment options for dealing with the current wave of disease. This review provides frontline clinicians with a pragmatic summary of the current state of the rapidly evolving evidence supporting emerging candidate therapeutics for COVID-19. Two main categories of pharmaceutical therapeutics are showing promise—those with antiviral activity directly addressing infection and those that counteract the inflammatory cytokine storm induced by severe disease. Preliminary results suggest that other approaches such as convalescent plasma therapy and lung radiation therapy may have some efficacy. The current clinical evidence for potential treatments is preliminary – often small retrospective series or early results from randomized trials – and the science is evolving rapidly. Long-term results from large, well-designed randomized trials will provide definitive evidence of therapeutic effectiveness and are likely months away. The trial landscape for promising therapies is described.
Abbreviations

CPT—convalescent plasma therapy
CQ—chloroquine
EC$_{50}$—half maximal effective concentration
HCQ—hydroxychloroquine
ICU—intensive care unit
IL6—interleukin 6
LPV/RTV—lopinavir/ritonavir
MERS—Middle East respiratory syndrome
RCT—randomized controlled trial
SARS—systemic acute respiratory syndrome
SARS-CoV-2—systemic acute respiratory syndrome coronavirus-2
Article highlights
1. Most emerging therapies for treatment of COVID-19 have antiviral activity for addressing infection directly or counteract the inflammatory cytokine storm induced by severe disease.
2. The currently available clinical evidence for promising emerging COVID-19 therapies provides rationale for continued investigation but is inconclusive regarding efficacy.
3. Accessible, randomized, controlled clinical trials for these therapies are underway and will be essential for measuring their efficacy.
Introduction

The novel systemic acute respiratory syndrome (SARS) coronavirus-2 (SARS-CoV-2), the causal agent of COVID-19, appeared in December 2019 in Wuhan, China, and its subsequent worldwide spread prompted the World Health Organization (WHO) to declare a global pandemic and international public health emergency.¹ As of June 29, 2020, over 10 million cases have been reported in 188 countries/regions across the world resulting in over 500,000 deaths.² High mortality and hospitalization rates of COVID-19, especially in older patients with comorbidities,³ have stressed global health systems. Historically, the clinical approach to newly emergent pandemic threats has been largely reactive due to the absence of established therapeutic interventions.⁴

In a pandemic, there are inherent challenges to conducting randomized clinical trials with the urgent need to decrease mortality. Treatment based on preliminary science has ethical implications and, in many cases, the opportunity to rigorously study treatments before the pandemic subsides is lost. The rigor of scientific evidence for clinical benefit must be balanced with the expediency of treatment need.

Numerous therapies with a wide variety of mechanisms have been proposed for treating COVID-19. The aim of this narrative review is to provide frontline clinicians with a pragmatic summary of the current state of the rapidly evolving evidence supporting emerging therapeutics for COVID-19. We describe the mechanism of action and provide a succinct summary of the science supporting each treatment strategy and the pipeline of clinical trials.
Methods

To capture rapidly emerging COVID-19 science, all publication types (e.g., peer-reviewed research, editorials, preprints) were included in this review. Evidence was identified primarily through a search for publications with a ‘treatment’ tag in the National Library of Medicine’s LitCovid literature hub5,6 through June 29, 2020. Review of citations within these articles identified additional relevant articles. Studies were selected if they contained clinical data on COVID-19 therapeutics with near-term availability. Clinical trial landscape assessment for emerging therapies was performed by searching ClinicalTrials.gov7 for recruiting/open interventional trials on June 29, 2020, using a condition/disease query of COVID-19, SARS-CoV-2, and 2019-nCoV.

Evidence for promising therapies

Treatment development for COVID-19 has focused on repurposing existing drugs targeting the virus directly or mitigating the excessive inflammatory response it triggers. Convalescent plasma therapy (CPT) and drugs that were used for similar diseases including SARS, Middle East respiratory syndrome (MERS), and Ebola have emerged as treatment options due to their known safety profiles and availability. The current evidence for the most promising COVID-19 emerging therapies identified in a LitCovid literature hub search of 5,788 total publications is reviewed below and summarized in Table 1.
Remdesivir

Remdesivir is an adenosine analogue developed to treat Ebola. Its effects derive from inhibition of viral replication and RNA synthesis.\textsuperscript{8, 9} Data supporting treatment of SARS-CoV-2 infection with remdesivir include established potency against coronaviruses in vitro\textsuperscript{8} and in mouse\textsuperscript{10} and primate\textsuperscript{11} models. In-vitro studies with SARS-CoV-2 measured a half maximal effective concentration (EC\textsubscript{50}) of 0.77μM and inhibition of infection in Huh-7 cells.\textsuperscript{12} Combination with emetine may enhance viral inhibition.\textsuperscript{13}

Clinically, multiple case reports and series from Canada, Europe, Japan, and the United States have provided early promising results of treatment with remdesivir, usually in combination with other agents.\textsuperscript{14-19} In the first reported double-blind, randomized, placebo-controlled trial (RCT) of remdesivir, the time to clinical improvement was similar to the control group but numerically shorter for patients treated within 10 days of symptom onset. This trial unfortunately did not attain the predetermined sample size due to containment of the outbreak in China.\textsuperscript{20} A global, double-blinded, randomized, placebo-controlled trial of remdesivir in 1,063 patients, funded by the National Institute of Allergy and Infectious Diseases, reported an 11-day median recovery time compared with 15 days for patients receiving the placebo.\textsuperscript{21} However, a randomized, multi-country, open-label trial of remdesivir treatment for 5 or 10 days in 397 patients with severe COVID-19 but not receiving mechanical ventilation determined no difference in 14-day clinical improvement between treatment groups on an ordinal scale (64% of patients improving vs. 54% in the 10-day group).\textsuperscript{22}

Favipiravir
Favipiravir’s antiviral properties are thought to arise from inhibition of viral RNA polymerase, halting the replication cycle.\textsuperscript{23,24} Reports of favipiravir’s efficacy in COVID-19 are limited to in-vitro studies determining an EC\textsubscript{50} of 61.88μM in Vero E6 cells,\textsuperscript{12} a nonrandomized before-after controlled open label trial versus lopinavir/ritonavir (LPV/RTV),\textsuperscript{25} and a non-peer-reviewed preprint of an open label randomized multicenter trial comparing arbidol therapy to favipiravir.\textsuperscript{26} In the before-after study, 91.43% of the 35 patients receiving favipiravir showed improvement in chest imaging and had a median time of viral clearance of 4 days compared with 62.2% of the 45 patients receiving LPV/RTV showing improvement in chest imaging and a median of 11 days for viral clearance. The randomized multicenter trial showed a 7-day clinical recovery rate (>72 hours normalization of temperature, respiratory rate, oxygen saturation and cough) of 71.43% and 55.86% for patients with mild or moderate disease treated with favipiravir or arbidol, respectively, but no difference in critically ill patients or those with hypertension and/or diabetes.

**Lopinavir (LPV)/Ritonavir (RTV)**

LPV/RTV inhibit the human immunodeficiency virus (HIV) 1 protease and is used in the treatment of HIV infection and acquired immune deficiency syndrome (AIDS). Reports of the potentially successful use of LPV/RTV in treatment of MERS\textsuperscript{27,28} and an ongoing clinical trial\textsuperscript{29} have led to hypotheses about its usefulness in treating COVID-19 and its widespread use with ribavirin in the management of COVID-19 in China. Demonstrated efficacy has been varied and in a mouse model of MERS, LPV/RTV demonstrated inferior reduction in viral load and severe lung pathology versus remdesivir.\textsuperscript{10}
Preliminary clinical data about LPV/RTV therapy in COVID-19 patients in China and Singapore have produced mixed results.\textsuperscript{30-32} Two retrospective studies of 97 and 42 patients found that mRNA conversion time was correlated with hospital length of stay in LPV/RTV treatment groups,\textsuperscript{33} and patients receiving LPV/RTV, arbidol, and interferon had a shorter time to return of normal body temperature and laboratory values.\textsuperscript{34} Triple combination therapy using LPV/RTV and interferon beta-1b in an open-label randomized trial of 86 patients resulted in a shorter median number of days to viral clearance (7 vs. 12 in patients treated with only LPV/RTV).\textsuperscript{35} Conversely, separate retrospective analyses of 134 and 50 patients receiving LPV/RTV, arbidol, or no antiviral therapy demonstrated no improvement in symptoms or viral clearance from treatment\textsuperscript{36,37} A 199-patient RCT of LPV/RTV in patients with severe COVID-19 also resulted in no benefit in time to clinical improvement or viral RNA load compared with controls but did demonstrate reduced intensive care unit (ICU) length of stay.\textsuperscript{38} Results from an RCT comparing treatment with LPV/RTV and arbidol in 44 patients with mild/moderate COVID-19 were reported in a non-peer-reviewed forum and showed little benefit in clinical outcomes\textsuperscript{39} as did a randomized trial of 22 patients comparing LPV/RTV to chloroquine (CQ).\textsuperscript{40} A study of LPV/RTV pharmacokinetics in 8 COVID-19 patients suggested that current doses are likely 60–120 fold too low at trough to achieve EC50 concentrations,\textsuperscript{41} perhaps explaining the overall lack of effect seen in studies to date.

**Immunomodulators**

Induction of an inflammatory cytokine storm is a well-described phenomenon in patients with SARS,\textsuperscript{42} and it has been observed in early investigations of SARS-CoV-2 infection.\textsuperscript{43,44} Consequently, the effects of immunomodulators on COVID-19 are being evaluated. Since
interleukin 6 (IL6) levels have been observed to be consistently elevated in patients with severe COVID-19,\textsuperscript{45-48} inhibition of the IL6-receptor with monoclonal antibodies such as tocilizumab and sarilumab are of great interest for the treatment of COVID-19. Janus kinase (JAK) inhibitors such as baracitinib and ruxolitinib are also being considered for treating COVID-19-associated cytokine storm. Baracitinib was identified as a candidate COVID-19 therapeutic agent through search of a knowledge graph generated in part by machine learning.\textsuperscript{49, 50} However, there are concerns about drug-induced lymphocytopenia that may limit the utility of this small molecule targeted agent in the management of COVID-19.\textsuperscript{51} Based on previous reports of possible benefits, including decreased mortality and shorter hospital stay, from properly prescribed systemic glucocorticoid therapy for critically ill patients with SARS,\textsuperscript{52, 53} glucocorticoid management of COVID-19 is also being explored.

A study of 21 patients in China receiving tocilizumab in addition to standard of care showed clinical improvements including fever resolution and improved oxygen saturation within 24 hours following treatment.\textsuperscript{54} One retrospective evaluation of 15 patients receiving tocilizumab showed reductions in C-reactive protein and IL6 levels in all patients except those who were critically ill and received only one dose.\textsuperscript{55} Retrospective analyses of 100\textsuperscript{56} and 85\textsuperscript{57} patients receiving tocilizumab plus lopinavir/ritonavir or hydroxychloroquine (HCQ) compared with lopinavir/ritonavir or HCQ alone found, respectively, that 25% of patients receiving tocilizumab experienced death/and or ICU admission and a hazard ratio (HR) for death of 0.035. In a retrospective study of 100 consecutive patients receiving tocilizumab in Italy, 77% of patients’ conditions stabilized or improved while in 23% their condition worsened.\textsuperscript{58} A prospective open,
single-arm multicenter study of 63 patients receiving tocilizumab demonstrated improvement in respiratory and laboratory parameters. In this same study, administration of tocilizumab within 6 days of admission was associated with increased likelihood of survival (HR 2.2). Conversely, a 21-patient retrospective analysis of tocilizumab treatment in Italy did not find reductions in ICU admission or 7-day mortality rates. Interestingly, a retrospective analysis of 78 patients receiving tocilizumab suggested that IL6 levels in hyperglycemic patients persisted at levels 5-fold higher than normoglycemic patients and that treatment failed to attenuate risk of severe outcomes in these patients.

Publication of in vitro experiments showing the JAK inhibitor baricitinib's ability to reduce viral load in human primary liver spheroids and a 4-patient case series demonstrating improvement in signs and symptoms including cough, fever, IL6 levels, and viral load seem to validate its identification as a potential therapeutic for COVID-19. Addition of baricitinib to LPV/RTV therapy in 12 Italian patients resulted in improvements to clinical and respiratory parameters in the following 2 weeks. A retrospective multicenter study in 191 patients showed 6% and 17% reductions in 2-week fatality rate and ICU admission in the baricitinib arm (baricitinib plus LPV/RTV) compared with controls (HCQ plus LPV/RTV). In a 41-patient, multicenter, single-blind, randomized trial of a different JAK inhibitor, ruxolitinib, patients receiving ruxolitinib had numerically faster, but not statistically significant, clinical improvements over patients receiving placebo plus standard of care. However, a retrospective study of 14 patients in Germany with progressive hyperinflammation resulting from COVID-19 showed a 58% decline in inflammation.
scores 7 days after treatment with ruxolitinib, and 76% of patients had clinical improvement on the WHO ordinal scale.\textsuperscript{66}

Preliminary studies of glucocorticoid therapy in COVID-19 to date present mixed results regarding their effects on mortality, clinical parameters, and length of stay.\textsuperscript{67} However, a non-peer reviewed publication of a 6,425-patient open-label RCT of low to moderate-dose dexamethasone showed reductions in 28-day mortality in one third of patients receiving mechanical ventilation and one fifth of patients on oxygen support without ventilation.\textsuperscript{68}

**Chloroquine and hydroxychloroquine**

HCQ and CQ are quinine analogs that have been widely used in the treatment of malaria and autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus. Their in-vitro antiviral properties have been known for decades\textsuperscript{69-71} and more recently have been studied in SARS-CoV.\textsuperscript{72} Repeated studies have shown that the in-vitro antiviral activity of CQ has failed to translate to clinical outcomes in other viral diseases (reviewed in\textsuperscript{73}). Double-blinded RCTs to date have failed to demonstrate CQ's efficacy as an antiviral in influenza, dengue, and chikungunya.\textsuperscript{74-76}

Both CQ and HCQ have significant (EC\textsubscript{50} of 5.47\textmu M and 0.72 \textmu M respectively) in-vitro activity against SARS-CoV-2.\textsuperscript{77, 78} Publication of a 30-patient RCT of HCQ in China showed no difference in time to viral clearance, body temperature, or radiological progression compared to conventional treatment.\textsuperscript{79} A manuscript describing a 150-patient open label RCT also found no difference in viral clearance through 28 days between patients treated with HCQ or standard of
care. However, post-hoc analyses suggest that symptom alleviation was faster in patients receiving HCQ when accounting for confounding from other antiviral therapies.\textsuperscript{80} No difference in mortality, ICU admission, or ventilation rates was observed with HCQ treatment in retrospective analyses of 368 US patients\textsuperscript{81} and 191 French patients\textsuperscript{82} who received HCQ, HCQ added to azithromycin, or who were unexposed to HCQ. Likewise, in a 1,376-patient observational study at a single hospital and a 1,438-patient multicenter retrospective analysis in New York, there was no significant association between HCQ use and intubation or death (hazard ratio 1.04)\textsuperscript{83} or HCQ and azithromycin use and mortality.\textsuperscript{84} The first randomized, double-blind, placebo-controlled study of postexposure prophylactic HCQ treatment showed no apparent decrease in incidence between treatment and placebo groups (11.8\% vs 14.3\%) in the 821 participants at moderate or high risk of exposure to COVID-19.\textsuperscript{85} In one open-label non-randomized trial in 36 French patients, HCQ treatment virologically cured 57\% of patients (100\% of patients when used in conjunction with azithromycin) within 6 days of treatment compared to 12.5\% of control patients.\textsuperscript{86} Although a follow-up study of azithromycin combined with HCQ in 80 additional French COVID-19 patients confirmed significant reductions in viral load and improved clinical outcomes\textsuperscript{87}, the first study has been criticized for a lack of randomization, patients dropped from analysis, and the chosen thresholds for determining viral presence.\textsuperscript{88,89} A statement from the International Society of Antimicrobial Chemotherapy indicated that the article didn’t meet their expected standards.\textsuperscript{90} Interestingly, a separate team’s efforts to replicate viral clearance in a 12-patient case series using HCQ azithromycin combination therapy found that only 20\% of patients using this treatment tested negative for SARS-CoV-2 at days 5 to 6 after treatment.\textsuperscript{91} However, a retrospective analysis of 1,061 patients
(95% with mild disease) by the same group whose studies have been questioned, showed a good clinical outcome (no death, hospitalization for 10 days or more, viral shedding, or transfer to ICU) in 91.7% of patients and mortality in 0.9%. A randomized trial of 22 patients comparing CQ to LPV/RTV, a retrospective analysis of 48 patients receiving HCQ compared with 502 patients receiving standard therapy, and a non-peer-reviewed pre-print describing a double-blinded RCT of HCQ therapy in 62 patients with mild disease also seem to indicate some benefit in time to clinical recovery or mortality from CQ or HCQ treatment.

As a result of their potentially severe toxicities, the safety of CQ and HCQ in COVID-19 is in question. In a retrospective analysis of 95 patients receiving CQ for COVID-19 in the Netherlands, 23% of patients had a QTc interval exceeding 500ms during treatment, but in France, less than 6% of 73 patients had prolonged QTc measurements greater than 500ms after HCQ + azithromycin treatment. One arm of a double-blind randomized trial of CQ in Brazil with dosing of 600mg twice daily was halted by the data safety monitoring board after 6 days as a result of QT prolongation. Fatality rates for the duration of the trial showed no difference to historical data from similar patients, and only 7% of patients tested negative for virus during that time. Pharmacokinetic simulations have highlighted potential safety concerns with current CQ and HCQ dosing and questioned their ability to achieve concentrations required for antiviral activity.

**Convalescent plasma therapy (CPT)**

Virus-specific antibodies present in CPT have been used as late-line treatments in recent epidemics including SARS, Ebola, H1N1 influenza, MERS, and throughout the history of
medicine. A retrospective study of therapeutic plasma exchange in patients with sepsis and multi-organ failure that is currently under peer-review suggests that for patients with pneumonia as the primary source of sepsis, this approach may improve mortality rates.

On March 24th, the US FDA made CPT available for use in patients with serious COVID-19 infections through emergency investigational new drug (IND) applications. Actual data on the use of CPT in COVID-19 to date is limited, but growing. Case series in China, Korea, Mexico, and the USA have demonstrated varying clinical improvement resulting from CPT, ranging from improvement in laboratory and respiratory parameters without change in overall status to improvements in viral clearance and status as determined by the WHO ordinal scale. Conversely, a retrospective study of 6 patients treated with CPT eliminated virus shedding in all patients within 3 days but only 1 patient ultimately survived. An open-label, multicenter, randomized clinical trial of 101 patients in China showed clinical improvement on a 6-point scale within 28 days of treatment for 51.9% of patients receiving CPT compared with 43.1% in the control group (P=0.26), but viral clearance was achieved in 87.2% of patients in the treatment group compared with 37.5% in the control group (P<0.001); interpretation of these results is limited, however, since the trial was terminated early due to containment of COVID-19 in the area. In all of these studies, patients treated with CPT also received other treatments, including antiviral therapies, so the contribution of CPT to patient recovery is currently unclear. However, a non-peer reviewed study of 5,000 patients receiving CPT as part of the US FDA Expanded Access Program resulted in a serious adverse event rate <1%, suggesting that CPT in COVID-19 appears to be safe.
Targeted therapeutics and vaccines

The development of novel drugs and vaccines targeting SARS-CoV-2 is a fundamental step in the control of the COVID-19 pandemic. A detailed review of these efforts is beyond the scope of this work but it is important to highlight that dozens of small molecule, biologic, and RNA-based therapies are being actively developed for the treatment of COVID-19 (reviewed in\(^\text{114}\)) and will be essential for containing future waves of disease. On June 1, 2020, a first of its class targeted COVID-19 therapy, LY-CoV555, a monoclonal antibody targeting SARS-CoV-2, began clinical evaluation in a randomized, double-blind, placebo controlled phase I clinical trial assessing its safety and tolerability in hospitalized patients with COVID-19.\(^\text{115}\) Likewise, COVID-19 vaccine development has unfolded at unprecedented scale and speed—as of June 24, 2020, over 150 active COVID-19 vaccine projects are underway, 16 of which have begun human testing.\(^\text{116}\) Development of effective COVID-19 vaccines is crucial for enabling long-term management of the pandemic.

Active clinical trials

As of June 29, 2020, an assessment of clinical trials for COVID-19 emerging therapies on ClinicalTrials.gov produced 1,154 search results. The number and type of trials for the therapies included in this review are summarized in Table 2. Emerging trials of note include the use of low-dose radiation therapy to suppress the cytokine storm and resultant pulmonary inflammation and edema\(^\text{117}\) as well as evaluation of ivermectin based on its in vitro anti-SARS-CoV-2 effects.\(^\text{118}\)
The scientific community has responded to the COVID-19 pandemic with rapid implementation and execution of well-designed and accessible RCTs (examples shown in Table 3). An illustrative example is the SOLIDARITY trial, a WHO-sponsored, adaptive RCT open to any patient with confirmed SARS-CoV-2 infection worldwide. Based on institutional drug availability, patients were initially randomized to standard of care or to any of 4 arms: remdesivir, CQ/HCQ, LPV/RTV, or LPV/RTV plus interferon beta-1a. Strengths of SOLIDARITY are the simplicity of eligibility criteria that enable enrollment of a large volume of patients along with a robust scientific methodology, electronic endpoint data capture, and an adaptive design to allow modification of treatment arms based on evolving evidence. An example of adaptation is the halting of the HCQ arm of SOLIDARITY on June 17, 2020 based on initial results not showing reduction in mortality compared with standard of care. Similarly, the NIH’s ORCHID trial of HCQ was halted after the data safety and monitoring board determined that HCQ was unlikely to be beneficial to hospitalized patients with COVID-19.

Conclusion

This review of available data about the efficacy and safety of emerging therapies for COVID-19 provides a few promising results, but the evidence base is growing and evolving rapidly. Based on preliminary clinical data and in-vitro studies, remdesivir is a leading antiviral candidate for the treatment of COVID-19. The results of CQ and HCQ clinical studies are conflicting, many involve confounding concurrent administration of antiviral therapies, and increasingly suggest limited, if any, benefit for the treatment of COVID-19. Similarly, reports about the use of
convalescent plasma, usually in late stage disease and after other treatments, provide some support for clinical efficacy. Preliminary results from the low to moderate-dose dexamethasone arm of the large RCT, RECOVERY, show reduced mortality in patients requiring oxygen and or ventilation support. These findings suggest that immunomodulatory therapies may play an important role in controlling severe COVID-19. However, more studies are needed to confirm the safety and efficacy of glucocorticoids and other immunosuppressive drugs for the treatment of SARS-CoV-2-associated cytokine storm, including timing, dose, and duration of these therapies.

Most publications from this review were of observational studies in patients who received more than one therapy and lacked control groups or randomization. Thus, it is impossible to know whether observed clinical improvements are the result of the treatment or may have occurred anyway. These studies do, however, provide the basis for estimation of effect sizes and evidence of safety to allow ethical enrollment in the RCTs that will definitively measure treatment safety and efficacy.

Clinicians, scientists, patients, and their families must be cautious about interpretation and application of early results. The rapid evolution of COVID-19 knowledge combined with amplification by the lay press has resulted in several misinterpretations and high-profile study retractions. Clinical trials of therapeutic, prophylactic, and preventive interventions are underway, and therapeutic development is being expedited by unprecedented collaboration and removal of unnecessary barriers in the scientific process. The actions of the scientific community in combating the COVID-19 pandemic provide hope that after the current global
health crisis, the acceleration of preventive, diagnostic, and therapeutic discoveries will become the “new normal” for science. This approach might be replicated for a wide variety of complex diseases in need of effective treatments and cures such as cancer, obesity, Alzheimer’s disease, diabetes, or opioid and alcohol addiction. The COVID-19 pandemic is a formidable healthcare challenge but also an opportunity to foster the collaboration of multiple stakeholders; utilization of technologies for big data management, storage, and sharing; and the rapid and continuous knowledge integration necessary to accelerate the bench to bedside process. In the long run, as a public health emergency of international concern, COVID-19 provides the necessary lessons for developing rapid learning health care systems that can help expedite the discovery of novel therapeutics and their efficient introduction into practice.
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### Tables

#### Table 1. Current evidence for COVID-19 emerging therapies

| Therapy                                | References by type of evidence | Mechanism                                                                 | Expected Therapeutic Action |
|----------------------------------------|---------------------------------|---------------------------------------------------------------------------|----------------------------|
| Remdesivir                             | Preclinical = 10, 11, 12, 13     | Adenosine analogue that causes termination of RNA synthesis               | Antiviral                  |
|                                        | Case Report/Series = 14, 15, 16, 17, 18, 19 |                                            |                            |
|                                        | Clinical Trial = 20, 21, 22      |                                            |                            |
| Favorpiravir                           | Preclinical = 12                | Selective inhibition of RNA polymerase                                     | Antiviral                  |
|                                        | Clinical Trial = 25, 26*        |                                            |                            |
| Lopinavir Ritonavir Combination        | Preclinical = 10                | Retroviral protease inhibitor                                              | Antiviral                  |
|                                        | Case Series = 30, 31, 33, 41    |                                            |                            |
|                                        | Cohort = 33, 34, 36, 37         |                                            |                            |
|                                        | Clinical Trial = 35, 38, 39*, 40 |                                            |                            |
| Tocilizumab/Baricitinib/Ruxolitinib/    | Preclinical = 49, 50, 62, 63     | Interleukin-6-receptor inhibitors/selective inhibitors of Janus Kinases (JAKs) | Anti-Inflammatory          |
| Dexamethasone                          | Case Series = 54, 62, 63        |                                            |                            |
|                                        | Cohort = 55, 56, 57, 58, 60, 61, 64, 66, 67 |                                            |                            |
|                                        | Clinical Trial = 59, 65, 68*     |                                            |                            |
| Chloroquine,                          | Preclinical = 77, 78, 98, 99     | Inhibition of viral replication and modulation of immune responses         | Antiviral/Anti-inflammatory |
| Hydroxychloroquine                     | Case series = 91                |                                            |                            |
|                                        | Cohort = 82, 83, 84, 90, 92, 93, 95, 96 |                                            |                            |
|                                        | Clinical Trial = 40, 79, 80, 85, 86, 87, 94*, 97 |                                            |                            |
| Convalescent Plasma                   | Case series = 103, 104, 105, 106, 107, 108, 109, 120 | Transfer of humoral immunity                                               | Anti-SARS-CoV-2 humoral immunity |
|                                        | Cohort = 111, 113*              |                                            |                            |
|                                        | Clinical Trial = 112            |                                            |                            |

* denotes non-peer-reviewed publications. SARS = severe acute respiratory syndrome
Table 2. Clinical trial landscape for COVID-19 emerging therapies

| Therapy                                    | Number of trials | Geography      | Randomized (%) | Blinding (%) |
|--------------------------------------------|------------------|----------------|----------------|--------------|
| Remdesivir                                 | 8                | Global         | 7 (88)         |              |
|                                            |                  |                |                | None 4 (50)  |
|                                            |                  |                |                | Single 0 (0) |
|                                            |                  |                |                | Multi 4 (50) |
|                                            |                  |                |                | None 11 (61) |
|                                            |                  |                |                | Single 1 (6) |
|                                            |                  |                |                | Multi 6 (36) |
|                                            |                  |                |                | None 17 (71) |
|                                            |                  |                |                | Single 2 (8) |
|                                            |                  |                |                | Multi 5 (21) |
| Favipiravir                                 | 18               | Global         | 18 (100)       |              |
|                                            |                  |                |                | None 11 (61) |
|                                            |                  |                |                | Single 1 (6) |
|                                            |                  |                |                | Multi 6 (36) |
| Lopinavir-Ritonavir                        | 24               | Global         | 21 (88)        |              |
|                                            |                  |                |                | None 17 (71) |
|                                            |                  |                |                | Single 2 (8) |
|                                            |                  |                |                | Multi 5 (21) |
| Tocilizumab/Baricitinib/Ruxolitinib/Sarilumab/Desamethasone | 64               | Global         | 44 (69)        |              |
|                                            |                  |                |                | None 65 (49) |
|                                            |                  |                |                | Single 10 (7) |
|                                            |                  |                |                | Multi 59 (44) |
|                                            |                  |                |                | None 62 (77) |
| Chloroquine, Hydroxychloroquine            | 134              | Global         | 123 (92)       |              |
|                                            |                  |                |                | None 12 (9)  |
|                                            |                  |                |                | Single 3 (2) |
|                                            |                  |                |                | Multi 17 (12) |
| Convalescent Plasma                        | 81               | Global         | 49 (60)        |              |
|                                            |                  |                |                | None 12 (9)  |
|                                            |                  |                |                | Single 3 (2) |
|                                            |                  |                |                | Multi 17 (12) |
| Ivermectin                                 | 26               | Global         | 24 (92)        |              |
|                                            |                  |                |                | None 12 (9)  |
|                                            |                  |                |                | Single 3 (2) |
|                                            |                  |                |                | Multi 17 (12) |
| Low-dose radiation                         | 12               | US, Italy, India, Spain, Iran | 3 (23)        |              |
|                                            |                  |                |                | None 11 (92) |
|                                            |                  |                |                | Single 1 (9) |
|                                            |                  |                |                | Multi 1 (8)  |
| Other                                      | 838              |                |                |              |

Total recruiting/open interventional trials (1,154) listed from a search of ClinicalTrials.gov on June 29, 2020, using a condition/disease query of COVID-19, SARS-CoV-2, and 2019-nCoV.
Table 3. Representative practical well-designed clinical trials on emerging COVID-19 therapies.

| Trial          | Geography (target enrollment) | Sponsor                                      | Therapeutic focus                        | Control   | Study Design/characteristics | Inclusion/exclusion criteria                                                                 | Selected Outcomes                                      |
|----------------|-------------------------------|----------------------------------------------|------------------------------------------|-----------|-----------------------------|------------------------------------------------------------------------------------------------|--------------------------------------------------------|
| SOLIDARITY     | Global (119)                  | World Health Organization (WHO)              | SoC + Remdesivir                         | SoC       | Phase III, adaptive, open label, RCT | ≥18 years and hospitalized with confirmed COVID-19                                           | Mortality, Hospital length of stay, Receipt of ventilation or intensive care |
| DiCoVeRy      | Europe (3,100)                | Inserm                                       | SoC + Remdesivir                         | SoC       | Phase III multicenter/country, adaptive, open label, RCT | ≥18 years and hospitalized with confirmed COVID-19 + SpO\(_2\) ≤94% or acute respiratory failure | Clinical status at day 15, Hospital length of stay, Mortality |
| RECOVERY       | UK (5,000)                    | University of Oxford                        | SoC + LPV/RTV                            | SoC       | Phase II/III, adaptive, open label, RCT | ≥18 years and hospitalized with confirmed COVID-19                                           | Mortality within 28 days of randomization, Hospital length of stay, Number of patients needing ventilation |
| HYCOVID       | France (1,300)                | University Hospital, Angers                  | HCQ, Dexamethasone                       | Placebo   | Phase III multicenter, double-blind, RCT | ≥18 years with COVID-19 diagnosed within previous 48 hours + ≥75 years OR SpO\(_2\) ≤94% OR FiO\(_2\) ≤30 mmHg or Electrocardiogram showing absence of QT interval prolongation | Mortality or need for intubation and mechanical ventilation within 14 days of inclusion and start of treatment, Clinical improvement at 14 and 28 days |
| ACTT          | Global (440)                  | National Institutes of Allergy and Infectious Disease (NIAID) | Remdesivir                              | Placebo   | Phase III multicenter, adaptive, double-blind, RCT | ≥18 years with COVID-19 diagnosed within previous 72 hours + radiographic infiltrates by imaging OR SpO\(_2\) ≤94% OR requiring supplemental oxygen OR requiring mechanical ventilation | Percentage of subjects reporting each severity rating on an 8-point ordinal scale at day 15, Hospital length of stay, 14- and 28-day mortality |
| COVACTA       | Global (330)                  | Hoffmann-La Roche                            | Tocilizumab                              | Placebo   | Phase III multicenter, double-blind, RCT | ≥18 years and hospitalized with confirmed COVID-19 and SpO\(_2\) ≤93% or PaO\(_2\) <300 mmHg | Clinical status assessed with 7-point ordinal scale at day 28, Incidence of mechanical ventilation 7, 14, 21, 28, and 60-day mortality |
| CONCOVID      | Netherlands (426)             | Erasmus Medical Center                       | COVID-19 Convalescent Plasma             | SoC       | Phase II/III, randomized single-blinded, comparative trial | ≥18 years and hospitalized with confirmed COVID-19, excluding patients with a “no ICU admission” or “no invasive ventilation” restriction | Overall mortality until hospital discharge or 60-day mortality, Hospital length of stay |

SoC = Standard of Care, CQ/HCQ = Chloroquine or Hydroxychloroquine, LPV/RTV = Lopinavir/Ritonavir, IFN = Interferon, RCT = randomized controlled trial, SpO\(_2\) = peripheral capillary oxygen saturation, FiO\(_2\) = fraction of inspired oxygen, PaO\(_2\) = partial pressure of oxygen, ICU = intensive care unit