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MAYO CLINIC

REVIEW

A Narrative Review of Emerging Therapeutics for COVID-19

Van C. Willis, PhD; Yull Arriaga, MD; Dilhan Weeraratne, PhD; Fredy Reyes, PhD; and Gretchen P. Jackson, MD, PhD

Abstract

The novel severe acute respiratory syndrome coronavirus 2, the causal agent of coronavirus disease 2019 (COVID-19), quickly spread around the world, resulting in the most aggressive pandemic experienced in more than 100 years. Research on 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 of publications with a "treatment" tag through June 29, 2020 in the National Library of Medicine's LitCovid literature hub, 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 of randomized trials—and the science is evolving rapidly. The long-term results from large, well-designed randomized controlled trials will provide definitive evidence for therapeutic effectiveness and are likely months away. The trial landscape for promising therapies is described.

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The novel severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2), the causal agent of coronavirus disease 2019 (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, more than 10 million cases have been reported in 188 countries/regions across the world, resulting in more than 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 because of the absence of established therapeutic interventions.[4]

In a pandemic, there are inherent challenges to conducting randomized, controlled trials (RCTs) 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 (eg, peer-reviewed

From the IBM Watson Health, Center for AI, Research, and Evaluation, Cambridge, MA (V.C.W., Y.A., D.W., F.R.), and Department of Pediatric Surgery, Vanderbilt University Medical Center, Nashville, TN (G.P.J).

ARTICLE HIGHLIGHTS

- Most emerging therapies for coronavirus disease 2019 have antiviral activity for addressing infection directly or counteract the inflammatory cytokine storm induced by severe disease.
- The currently available clinical evidence for promising emerging coronavirus disease 2019 therapies provides rationale for continued investigation but is inconclusive regarding efficacy.
- Accessible, randomized, controlled trials of these therapies are underway and will be essential for measuring their efficacy.

research, editorials, and 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 hub[5,6] through June 29, 2020. A 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. A clinical trial landscape assessment for emerging therapies was performed by searching ClinicalTrials.gov[7] for recruiting/open interventional trials on June 29, 2020, using a condition/disease query of COVID-19, SARS-CoV-2, and 2019 novel coronavirus (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 because of 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 5788 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.[8,9] Data supporting treatment of SARS-CoV-2 infection with remdesivir include established potency against coronaviruses in vitro[8] and in mouse[10] and primate[11] models. In vitro studies with SARS-CoV-2 measured a half-maximal effective concentration (EC_{50}) of 0.77 μM and inhibition of infection in Huh-7 cells.[12] Combination with emetine may enhance viral inhibition.[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.[14-19] In the first reported double-blind, RCT of remdesivir, the time to clinical improvement was similar to the control group (hazard ratio, 1.27, 95% confidence interval, 0.89 to 1.80) but numerically shorter for patients treated within 10 days of symptom onset (hazard ratio, 1.52, 95% confidence interval, 0.95 to 2.43). This trial unfortunately did not attain the predetermined sample size owing to containment of the outbreak in China.[20] A global, double-blind, RCT of remdesivir in 1063 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 placebo ($P<.001$).[21] However, a randomized, multicountry, 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, $P=.14$).[22]

FAVIPIRAVIR

Favipiravir's antiviral properties are thought to arise from inhibition of viral RNA polymerase, halting the replication cycle.[23,24] Reports on favipiravir's efficacy in COVID-19 are limited to in vitro studies determining an EC_{50} of 61.88 μM in Vero E6 cells,[12] a nonrandomized, before-after controlled, open-label trial comparing lopinavir/ritonavir (LPV/RTV) with favipiravir,[25] and a non—peer-reviewed preprint of an open-label, randomized, multicenter trial comparing arbidol therapy with favipiravir.[26] In the before-after study, 91.43% of the 35 patients receiving favipiravir

TABLE 1. Current Evidence for COVID-19 Emerging Therapies[a]

Therapy	References by type of evidence	Mechanism	Expected therapeutic action
Remdesivir	Preclinical: 10, 11, 12, 13 Case report/series: 14, 15, 16, 17, 18, 19 Clinical trial: 20, 21, 22	Adenosine analogue that causes termination of RNA synthesis	Antiviral
Favipiravir	Preclinical: 12 Clinical trial: 25, 26[b]	Selective inhibition of RNA polymerase	Antiviral
Lopinavir/ritonavir	Preclinical: 10 Case series: 30, 31, 32, 41 Cohort: 33, 34, 36, 37 Clinical trial: 35, 38, 39, 40	Retroviral protease inhibitor	Antiviral
Tocilizumab/baricitinib/ruxolitinib/dexamethasone	Preclinical: 49, 50, 62 Case series: 54, 62, 63 Cohort: 55, 56, 57, 58, 60, 61, 64, 66, 67 Clinical trial: 59, 65, 68	Interleukin 6 receptor inhibitor/selective inhibitors of Janus kinases/modulation of immune responses	Anti-inflammatory
Chloroquine, hydroxychloroquine	Preclinical: 77, 78, 98, 99 Case series: 91 Cohort: 81, 82, 83, 84, 92, 93, 95, 96 Clinical trial: 40, 79, 80, 85, 86, 87, 94,[b] 97	Inhibition of viral replication and modulation of immune responses	Antiviral/anti-inflammatory
Convalescent plasma	Case series: 103, 104, 105, 106, 107, 108, 109, 110 Cohort: 111, 113 Clinical trial: 112	Transfer of humoral immunity	Anti–SARS-CoV-2 humoral immunity

[a]COVID-19 = coronavirus disease 2019; SARS-CoV-2 = severe acute respiratory distress syndrome coronavirus 2.
[b]Non–peer-reviewed publications.

exhibited improvement in chest imaging and had a median time of viral clearance of 4 days compared with 62.2% (P=.004) of the 45 patients receiving LPV/RTV exhibiting improvement in chest imaging and a median of 11 days for viral clearance (P<.001). The randomized multicenter trial reported a 7-day clinical recovery rate (>72 hours normalization of temperature, respiratory rate, oxygen saturation, and cough) of 71.43% and 55.86% (P=.0199) 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 (P=.4712 and P=.7704).

LOPINAVIR/RITONAVIR

Lopinavir/ritonavir inhibit the human immunodeficiency virus type 1 protease and are used in the treatment of human immunodeficiency virus infection and AIDS. Reports of the potentially successful use of LPV/RTV in the treatment of MERS[27,28] and an ongoing clinical trial[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. The reported efficacy has been varied, and in a mouse model of MERS, LPV/RTV was able to only slightly reduce viral load without impacting other disease parameters.[10]

Preliminary clinical data on LPV/RTV therapy in patients with COVID-19 in China and Singapore have suggested mixed results.[30-32] Two retrospective studies of 97 and 42 patients found that messenger RNA conversion time was correlated with hospital length of stay in LPV/RTV treatment groups (P=.0215 and P=.012),[33] and patients receiving LPV/RTV, arbidol, and interferon had a shorter time to return to normal body temperature (P=.0364) and laboratory values.[34] Triple combination therapy using LPV/RTV and interferon β-1b in an open-label randomized

trial of 86 patients resulted in a shorter median number of days to viral clearance (7 vs 12 (P=.0010) in patients treated with only LPV/RTV).[35] Conversely, separate retrospective analyses of 134 and 50 patients receiving LPV/RTV, arbidol, or no antiviral therapy revealed no improvement in symptoms or viral clearance from treatment (P>.05).[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 (P=.09) or viral RNA load compared with controls but did report reduced intensive care unit (-5 days, 95% confidence interval, -9 to 0) (ICU) length of stay.[38] The results of an RCT comparing treatment with LPV/RTV and arbidol in 86 patients with mild/moderate COVID-19 indicated little benefit in clinical outcomes[39] as did a randomized trial in 22 patients comparing LPV/RTV with chloroquine (CQ).[40] A study of LPV/RTV pharmacokinetic properties in 8 patients with COVID-19 suggested that current doses are likely 60- to 120-fold too low at trough to achieve EC_{50} concentrations,[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,[42] and it has been observed in early investigations of SARS-CoV-2 infection.[43,44] Consequently, the effects of immunomodulators on COVID-19 are being evaluated. Because interleukin 6 (IL-6) levels have been observed to be consistently elevated in patients with severe COVID-19,[45-48] inhibition of the IL-6 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 baricitinib and ruxolitinib are also being considered for treating COVID-19–associated cytokine storm. Baricitinib was identified as a candidate COVID-19 therapeutic agent through search of a knowledge graph generated in part by machine learning.[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.[51] On the basis of previous reports of possible benefits, including decreased mortality and shorter hospital stay, of properly prescribed systemic glucocorticoid therapy for critically ill patients with SARS,[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 found clinical improvements including fever resolution and improved oxygen saturation within 24 hours of treatment.[54] One retrospective evaluation of 15 patients receiving tocilizumab found reductions in C-reactive protein and IL-6 levels in all patients except those who were critically ill and received only 1 dose.[55] Retrospective analyses of 100[56] and 85[57] patients receiving tocilizumab plus LPV/RTV or hydroxychloroquine (HCQ) compared with LPV/RTV or HCQ alone, respectively, found that 25% of patients receiving tocilizumab experienced death and/or ICU admission and a hazard ratio for death of 0.035 (95% confidence interval, 0.004 to 0.347; P=.004). 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.[58] A prospective, open, single-arm, multicenter study of 63 patients receiving tocilizumab reported improvement in respiratory and laboratory parameters. In this same study, administration of tocilizumab within 6 days of admission was associated with an increased likelihood of survival (hazard ratio, 2.2, 95% confidence interval, 1.3 to 6.7; P<.05).[59] Conversely, a 21-patient retrospective analysis of tocilizumab treatment in Italy did not find reductions in ICU admission (P=.22) or 7-day mortality rates (P=.84).[60] Interestingly, a retrospective analysis of 78 patients receiving tocilizumab suggested that IL-6 levels in patients with hyperglycemia persisted at levels 5-fold higher than those in patients with normoglycemia and that treatment failed to attenuate the risk of severe outcomes in these patients.[61]

Publication of in vitro experiments establishing the JAK inhibitor baricitinib's ability to reduce viral load in human primary liver spheroids and a 4-patient case series exhibiting improvement in signs and symptoms including cough, fever, IL-6 level, and viral load seem to validate its identification as a potential therapeutic for COVID-19.[62] Addition of baricitinib to LPV/RTV therapy in 12 Italian

patients resulted in improvements in clinical and respiratory parameters in the following 2 weeks.[63] A retrospective multicenter study of 191 patients reported 6% and 17% reductions in 2-week fatality rate (P=.010) and ICU admission (P=.0001) in the baricitinib arm (baricitinib plus LPV/RTV) compared with the control arm (HCQ plus LPV/RTV).[64] 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 (P=.147), time to clinical improvement than did patients receiving placebo plus standard of care.[65] However, a retrospective study of 14 patients in Germany with progressive hyperinflammation due to COVID-19 reported a 58% decline in inflammation scores 7 days after treatment with ruxolitinib (P<.01) and 76% of patients had clinical improvement on the WHO ordinal scale.[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.[67] However, a 6425-patient open-label RCT of low- to moderate-dose dexamethasone reported reductions in 28-day mortality in one-third of patients receiving mechanical ventilation (rate ratio, 0.64; 95% confidence interval, 0.51 to 0.81) and one-fifth of patients on oxygen support without ventilation (rate ratio, 0.82; 95% confidence interval, 0.72 to 0.94).[68]

CHLOROQUINE AND HYDROXYCHLOROQUINE

Hydroxychloroquine and CQ are quinine analogues 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[69-71] and more recently have been studied in SARS-CoV.[72] Repeated studies have found that the in vitro antiviral activity of CQ has failed to translate to clinical outcomes in other viral diseases (reviewed in reference 73). Double-blind RCTs to date have failed to find CQ's efficacy as an antiviral in influenza, dengue, and chikungunya.[74-76]

Both CQ and HCQ have substantial (EC_{50} of 5.47 and 0.72 μM, respectively) in vitro activity against SARS-CoV-2.[77,78] A publication of a 30-patient RCT of HCQ in China reported no difference in time to viral clearance, body temperature, or radiological progression compared to conventional treatment (P>.05).[79] An article describing a 150-patient open-label RCT also reported no difference in viral clearance through 28 days between patients treated with HCQ and those treated with standard of care (P=0.34).[80] No difference in mortality, ICU admission, or ventilation rates was observed with HCQ treatment in retrospective analyses of 368 US patients (P>.05)[81] and 191 French patients (hazard ratio, 0.9, 95% confidence interval, 0.4 to 2.1)[82] who received HCQ or HCQ added to azithromycin or who were unexposed to HCQ. Likewise, in a 1376-patient observational study at a single hospital and a 1438-patient multicenter retrospective analysis in New York, there was no significant association between HCQ use and intubation or death (hazard ratio, 1.04, 95% confidence interval, 0.82 to 1.32)[83] or HCQ and azithromycin use and mortality.[84] The first double-blind, RCT of postexposure prophylactic HCQ treatment found no apparent decrease in incidence between treatment and placebo groups (11.8% vs 14.3%; P=.35) in 821 participants at a moderate or high risk of exposure to COVID-19.[85] In an open-label nonrandomized 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 with 12.5% of control patients (P<.001).[86] Although a follow-up study of azithromycin combined with HCQ in 80 additional French patients with COVID-19 confirmed considerable reductions in viral load and improved clinical outcomes,[87] the first study has been criticized for a lack of randomization, patients dropped from analysis, and the chosen thresholds for determining viral presence.[88,89] A statement from the International Society of Antimicrobial Chemotherapy indicated that the article did not meet their expected standards.[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.[91] However, a

retrospective analysis of 1061 patients (95% with mild disease) by the same group whose studies have been questioned revealed a good clinical outcome (no death, hospitalization for ≥10 days, viral shedding, or transfer to the ICU) in 91.7% of patients and mortality in 0.9%.[92] A randomized trial of 22 patients comparing CQ with LPV/RTV,[40] a retrospective analysis of 48 patients receiving HCQ compared with 502 patients receiving standard therapy,[93] and a non—peer-reviewed preprint describing a double-blind 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.[94] Of note, one large study suggesting treatment with CQ or HCQ increases risk of in-hospital mortality was retracted when a full audit of the primary dataset could not be completed.[95]

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 corrected QT interval exceeding 500 ms during treatment,[96] but in France, less than 6% of 73 patients had corrected QT measurements greater than 500 ms after HCQ plus azithromycin treatment.[97] One arm of a double-blind randomized trial of CQ in Brazil with a dosage of 600 mg 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 were not different from historical data from similar patients, and only 7% of patients tested negative for virus during that time.[98] Pharmacokinetic simulations have highlighted potential safety concerns with current CQ and HCQ dosing and questioned their ability to achieve concentrations required for antiviral activity.[99,100]

CONVALESCENT PLASMA THERAPY

Virus-specific antibodies present in CPT have been used as late-line treatments in recent epidemics including SARS, Ebola, H1N1 influenza, and MERS and throughout the history of medicine.[101] A retrospective study of therapeutic plasma exchange in patients with sepsis and multiorgan 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.[102]

On March 24, the US Food and Drug Administration made CPT available for use in patients with serious COVID-19 infections through emergency investigational new drug applications.[103] Actual data on the use of CPT in COVID-19 to date are limited, but increasing. Case series in China, Korea, Mexico, and the United States have reported varying clinical improvement due to 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.[104-111] 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.[112] An open-label, multicenter, randomized clinical trial of 101 patients in China reported 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=.26), but viral clearance was achieved in 87.2% of patients in the treatment group compared with 37.5% in the control group (P<.001); interpretation of these results is limited, however, because the trial was terminated early because of containment of COVID-19 in the area.[113] In all 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 study of 5000 patients receiving CPT as part of the US Food and Drug Administration Expanded Access Program resulted in a serious adverse event rate less than 1%, suggesting that CPT in COVID-19 appears to be safe.[114]

TARGETED THERAPEUTICS AND VACCINES

The development of novel drugs and vaccines targeting SARS-CoV-2 is a fundamental step in controlling 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 reference [115]) 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 double-blind, randomized, placebo-controlled, phase I clinical trial assessing its safety and tolerability in hospitalized patients with COVID-19.[116] Likewise, COVID-19 vaccine development has unfolded at an unprecedented scale and speed—as of June 24, 2020, more than 150 active COVID-19 vaccine projects are underway, 16 of which have begun human testing.[117] 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 1154 search results. The number and type of trials of 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[118] as

TABLE 2. Clinical Trial Landscape for COVID-19 Emerging Therapies[a,b]

Therapy	No. of trials	Geography	Randomized (%)	Blinding (%)	
Remdesivir	8	Global	7 (88)	None	4 (50)
				Single	0 (0)
				Multi	4 (50)
Favipiravir	18	Global	18 (100)	None	11 (61)
				Single	1 (6)
				Multi	6 (33)
Lopinavir/ritonavir	24	Global	21 (88)	None	17 (71)
				Single	2 (8)
				Multi	5 (21)
Tocilizumab/baricitinib/ruxolitinib/sarilumab/dexamethasone	64	Global	44 (69)	None	48 (75)
				Single	1 (2)
				Multi	15 (23)
Chloroquine, hydroxychloroquine	134	Global	123 (92)	None	65 (49)
				Single	10 (7)
				Multi	59 (44)
Convalescent plasma	81	Global	49 (60)	None	62 (77)
				Single	2 (2)
				Multi	17 (21)
Ivermectin	26	Global	24 (92)	None	12 (46)
				Single	3 (12)
				Multi	11 (42)
Low-dose radiation	12	United States, Italy, India, Spain, Iran	3 (25)	None	11 (92)
				Single	0 (0)
				Multi	1 (8)
Other	838				

[a]COVID-19 = coronavirus disease 2019; SARS-CoV-2 = severe acute respiratory distress syndrome coronavirus 2; 2019-nCoV = 2019 novel coronavirus.

[b]Total recruiting/open interventional trials (1154) 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 of Emerging COVID-19 Therapies

Trial	Geography (target enrollment)	Sponsor	Therapeutic focus	Control	Study design/ characteristics	Inclusion/exclusion criteria	Selected outcomes
SOLIDARITY[120]	Global	World Health Organization	SoC + remdesivir SoC + CQ/HCQ SoC + LPV/RTV SoC + LPV/RTV + IFN β-1a	SoC	Phase III, adaptive, open-label RCT	≥18 y and hospitalized with confirmed COVID-19	Mortality Hospital length of stay Receipt of ventilation or intensive care
Trial of Treatments for COVID-19 in Hospitalized Adults (DisCoVeRy) (ClinicalTrials.gov identifier: NCT04315948)	Europe (3100)	Inserm	SoC + remdesivir SoC + LPV/RTV SoC + IFN β-1a SoC + HCQ	SoC	Phase III multicenter/ country, adaptive, open-label RCT	≥18 y and hospitalized with confirmed COVID-19 + SpO_2 ≤94% or acute respiratory failure	Clinical status at day 15 Hospital length of stay Mortality
Randomised Evaluation of COVID-19 therapy (RECOVERY) Trial (International Clinical trials Registry Platform identifier: ISRCTN50189673)	United Kingdom (5000)	University of Oxford	SoC + LPV/RTV SoC + IFN β-1a SoC + HCQ SoC + dexamethasone	SoC	Phase II/III, adaptive, open-label RCT	≥18 y and hospitalized with confirmed COVID-19	Mortality within 28 d of randomization Hospital length of stay Number of patients needing ventilation
Hydroxychloroquine Versus Placebo in COVID-19 Patients at Risk for Severe Disease (HYCOVID) (ClinicalTrials.gov identifier: NCT04325893)	France (1300)	University Hospital Angers	HCQ	Placebo	Phase III, multicenter, double-blind RCT	≥18 y with COVID-19 diagnosed within previous 48 h + ≥75 y or SpO_2 ≤94% or FiO_2 ≤300 mm Hg Electrocardiogram showing the absence of QT interval prolongation	Mortality or need for intubation and mechanical ventilation within 14 d of inclusion and initiation of treatment Clinical improvement at 14 and 28 d
Adaptive COVID-19 Treatment Trial (ACTT) (ClinicalTrials.gov identifier: NCT04280705)	Global (440)	National Institute of Allergy and Infectious Diseases	Remdesivir	Placebo	Phase III, multicenter, adaptive, double-blind RCT	≥18 y with COVID-19 diagnosed within previous 72 h + radiographic infiltrates by imaging or SpO_2 ≤94% or requiring supplemental oxygen or requiring mechanical ventilation	Percentage of participants reporting each severity rating on an 8-point ordinal scale at day 15 Hospital length of stay 14- and 28-d mortality

Continued on next page

TABLE 3. Continued

Trial	Geography (target enrollment)	Sponsor	Therapeutic focus	Control	Study design/ characteristics	Inclusion/exclusion criteria	Selected outcomes
A Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients With Severe COVID-19 Pneumonia (COVACTA) (ClinicalTrials.gov identifier: NCT04320615)	Global (330)	Hoffmann-La Roche	Tocilizumab	Placebo	Phase III, multicenter, double-blind RCT	≥18 y and hospitalized with confirmed COVID-19 + SpO_2 ≤93% or PaO_2 <300 mm Hg	Clinical status assessed with a 7-point ordinal scale at day 28 Incidence of mechanical ventilation 7, 14, 21, 28, and 60-d mortality
Convalescent Plasma as Therapy for Covid-19 Severe SARS-CoV-2 Disease (CONCOVID Study) (ClinicalTrials.gov identifier: NCT04342182)	The Netherlands (426)	Erasmus Medical Center	COVID-19 convalescent plasma	SoC	Phase II/III, randomized single-blind, comparative trial	≥18 y 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-d Hospital length of stay

COVID-19 = coronavirus disease 2019; CQ/HCQ = chloroquine or hydroxychloroquine; FiO_2 = fraction of inspired oxygen; ICU = intensive care unit; IFN = interferon; LPV/RTV = lopinavir/ritonavir; PaO_2 = partial pressure of oxygen; RCT = randomized controlled trial; SoC = standard of care; SpO_2 = peripheral capillary oxygen saturation.

well as evaluation of ivermectin based on its in vitro anti—SARS-CoV-2 effects.[119]

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,[120] a WHO-sponsored, adaptive RCT open to any patient with confirmed SARS-CoV-2 infection worldwide. On the basis of institutional drug availability, patients were initially randomized to standard of care or to any of the 4 arms: remdesivir, CQ/HCQ, LPV/RTV, or LPV/RTV plus interferon β-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 end point data capture, and an adaptive design to allow the modification of treatment arms on the basis of evolving evidence. An example of adaptation is the halting of the HCQ arm of SOLIDARITY on June 17, 2020, on the basis of the initial results not indicating reduction in mortality compared with standard of care.[120] Similarly, the National Institutes of Health's Outcomes Related to COVID-19 treated with hydroxychloroquine among inpatients with symptomatic Disease study (ORCHID) was halted after the data safety and monitoring board determined that HCQ was unlikely to be beneficial to hospitalized patients with COVID-19.[121]

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. According to 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 of the use of convalescent plasma, usually in late-stage disease and after other treatments, provide some support for clinical efficacy. The preliminary results of the low- to moderate-dose dexamethasone arm of the Randomised Evaluation of COVID-19 Therapy (RECOVERY) Trial indicate 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 of patients who received more than 1 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 the 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 disease, diabetes, or opioid and alcohol addiction. The COVID-19 pandemic is a formidable health care 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.

Abbreviations and Acronyms: **COVID-19** = coronavirus disease 2019; **CPT** = convalescent plasma therapy; **CQ** = chloroquine; **EC_{50}** = half-maximal effective concentration; **HCQ** = hydroxychloroquine; **ICU** = intensive care unit; **IL-6** = interleukin 6; **JAK** = Janus kinase; **LPV/RTV** = lopinavir/ritonavir; **MERS** = Middle East respiratory syndrome; **RCT** = randomized controlled trial; **SARS** = severe acute respiratory syndrome; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus 2; **WHO** = World Health Organization

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Correspondence: Address to Van C. Willis, PhD, IBM Watson Health, Center for AI, Research, and Evaluation, 75 Binney St, Cambridge, MA 02142 (vcwillis@us.ibm.com).

ORCID

Van C. Willis: https://orcid.org/0000-0001-5577-0545;
Yull Arriaga: https://orcid.org/0000-0002-7229-2028

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