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Treatment Considerations for COVID-19: A Critical Review of the Evidence (or Lack Thereof)

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Abstract

The novel severe acute respiratory syndrome coronavirus 2 is causing a worldwide pandemic that may lead to a highly morbid and potentially fatal coronavirus disease 2019 (COVID-19). There is currently no drug that has been proven as an effective therapy for COVID-19. Several candidate drugs are being considered and evaluated for treatment. This includes clinically available drugs, such as chloroquine, hydroxychloroquine, and lopinavir/ritonavir, which are being repurposed for the treatment of COVID-19. Novel experimental therapies, such as remdesivir and favipiravir, are also actively being investigated for antiviral efficacy. Clinically available and investigational immunomodulators, such as the interleukin 6 inhibitors tocilizumab and sarilumab and the anti—granulocyte-macrophage colony-stimulating factor lenzilumab, are being tested for their anticipated effect in counteracting the pro-inflammatory cytokine environment that characterizes severe and critical COVID-19. This review article examines the evidence behind the potential use of these leading drug candidates for the treatment of COVID-19. The authors conclude, based on this review, that there is still no high-quality evidence to support any of these proposed drug therapies. The authors, therefore, encourage the enrollment of eligible patients to multiple ongoing clinical trials that assess the efficacy and safety of these candidate therapies. Until the results of controlled trials are available, none of the suggested therapeutics is clinically proven as an effective therapy for COVID-19.

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In December 2019, a novel coronavirus outbreak was reported from Wuhan in the Hubei province of China. As of April 16, 2020, the virus has infected more than 2,090,000 people worldwide, resulting in more than 139,000 deaths.[1] Initially called novel coronavirus, it was officially named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) because of its similarities with the agent that caused the severe acute respiratory syndrome (SARS) outbreak in 2003.[2] Severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome—related coronavirus (MERS), and SARS-CoV-2 belong to the Genus *betacoronavirus* and are agents of respiratory infections in humans.

The infection caused by SARS-CoV-2 manifests as coronavirus disease 2019 (COVID-19). The majority of patients infected with SARS-CoV-2 either remain asymptomatic or demonstrate mild symptoms and recover from their illness. The most common clinical presentation is pneumonia with symptoms of fever, dry cough, and shortness of breath.[3] Anosmia, dysgeusia, and diarrhea have been reported.[4] Approximately 20% to 30% of patients require intensive care for respiratory support, and more than 15% of patients with severe pneumonia develop acute respiratory distress syndrome (ARDS) (Figure 1).[5,6]

There is currently no proven drug for the treatment of COVID-19. The standard of

care is supportive measures, aimed at managing fever, dehydration, and constitutional and other clinical symptoms. Because of the morbid and potentially fatal nature of COVID-19, there have been efforts to repurpose other clinically available drugs based on antiviral activities that have either been shown in vitro or proposed due to the agents' mechanism of action. Novel and experimental drugs with potential antiviral properties are also being considered. Finally, therapies that modulate the hyperinflammatory response of the host are being investigated (Table).[7-28] Antiviral drugs are believed to be useful early in the course of the disease when it is mediated by active viral replication. Immunomodulating agents are generally being evaluated for use during the later pro-inflammatory process, usually manifesting as clinical deterioration in the second week after symptom onset.

In this article, we aim to provide an objective review of the evidence behind the proposed drug therapies for COVID-19. Electronic search in PubMed, LitCovid, Embase, Google Scholar, and clinicaltrials. gov databases was conducted. Search terms included SARS-CoV-2, COVID-19, 2019-nC0V,

ARTICLE HIGHLIGHTS

- Antiviral and immunomodulatory therapies, investigational and re-purposed, for the management of coronavirus disease-2019 are reviewed. The use of these drugs should be under clinical trial protocols.
- The mechanisms of action for treatment options being considered for coronavirus disease 2019 and their potential toxicities are discussed.
- A hypothetical protocol that may serve as a starting point for health care providers to develop institution-specific protocols based on available resources.

and individual drug names. Articles published in English were reviewed and relevant references were checked. The information in this review is only as current as of the time this article is written (April 16, 2020) since new data is anticipated to emerge during this rapidly evolving pandemic. Based on the currently available information, health care institutions are encouraged to create local protocols based on available resources. A hypothetical protocol that may serve as a starting point is depicted in Figure 2.
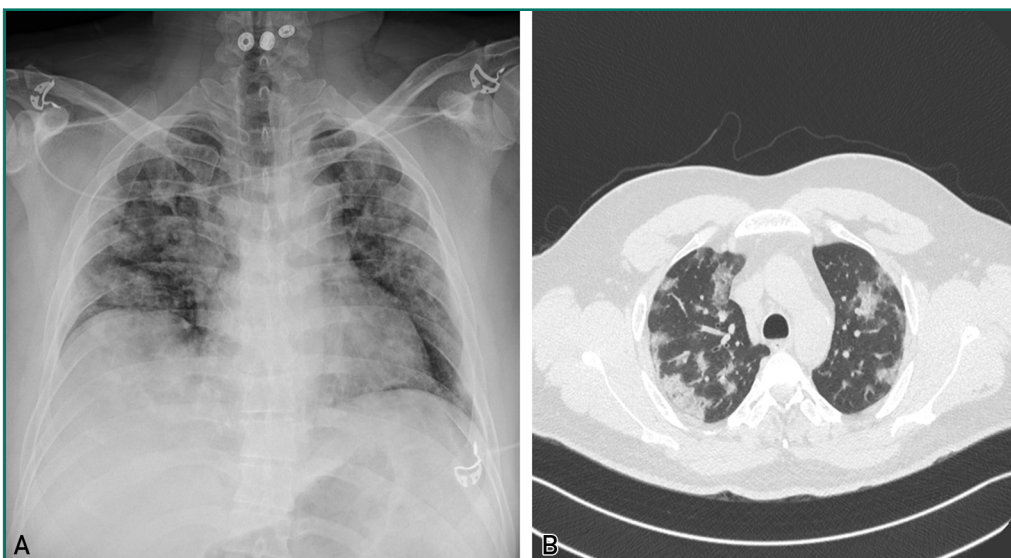

FIGURE 1. A, Chest x-ray showing diffuse bilateral opacities in a patient with coronavirus disease 2019 and acute respiratory distress syndrome. B, Computed tomography scan of the chest showing peripherally based ground-glass opacities and pulmonary infiltrates.

TABLE. Candidate Therapies for the Management of Coronavirus Disease 2019[a]

Drug	Proposed mechanism of action		Evidence for SARS-CoV-2	Clinical trials[7]
Hydroxychloroquine and chloroquine	Blocks viral entry by increasing endosomal pH and inhibiting viral fusion to the cell membrane Decreases affinity of ACE2 receptor for SARS-Cov-2 by impairing terminal glycosylation of ACE2	In vitro Clinical	Wang et al: Chloroquine affected entry and post-entry stages of infection. 500 mg per day of chloroquine would achieve EC_{50}.[8] Yao et al: Hydroxychloroquine was more potent (EC_{50} of 0.72 μM) than chloroquine (EC_{50} of 5.47 μM).[9] Liu et al: Chloroquine had lower EC_{50} compared with hydroxychloroquine.[10] Gao et al: Preliminary data from 100 patients demonstrated chloroquine was better than control (peer review data not available).[11] Gautret et al: Hydroxychloroquine was better than control at viral eradiation. This effect was magnified by addition of azithromycin. There are major limitations in the study analysis.[12] Gautret et al: Confirmed the efficacy of hydroxychloroquine and azithromycin combination but the study did not have a control group.[13] Molina et al: 8/10 (80%) of patients had positive SARS-CoV-2 PCR on days 5-6 after treatment with a combination of hydroxychloroquine and azithromycin. The study did not have a control group.[14] Chen et al: Hydroxychloroquine was associated with better clinical outcome compared with control group (80.6% versus 54.8%, respectively). The study is pending peer-review.[15]	NCT04261517 NCT04308668 NCT04323527 NCT04304053 NCT04307693
Favipiravir	RNA-dependent RNA polymerase inhibitor	In vitro Clinical	Wang et al: EC_{50} of favipiravir was 61.88 which was higher than EC_{50} for remdesivir and chloroquine.[8] Cai et al: The study has been temporarily removed. Open label study comparing favipiravir and LPV/r. Favipiravir was associated with shorter time to viral clearance (median 4 d vs 11 d, $P<.001$) and significant improvement in chest imaging (improvement rate 91.43% versus 62.22%, $P=.004$).[16]	NCT04310228 NCT04303299
Lopinavir/ritonavir	Lopinavir is a viral protease inhibitor that blocks viral replication Ritonavir blocks CYP3A4 thereby boosting concentration of lopinavir	Clinical	Bhatnagar et al, Young et al, Han et al, Lim et al, Wang et al: Case reports or case series of patients treated with LPV/r along with other therapies including Chinese herbal therapies.[17-21] Cao et al: Randomized open label study that showed that LPV/r combination was not significantly better than standard of care.[22] Deng et al: combination of arbidol with LPV/r was significantly better than LPV/r alone for nasopharyngeal swab test conversion.[23]	NCT04307693 NCT04276688
Remdesivir	RNA-dependent RNA polymerase inhibitor	In vitro Clinical	Wang et al: Remdesivir has potent activity against SARS-CoV-2 infected Vero cells[8] Holshue et al: First successful use of remdesivir in COVID-19 patient in the United States.[24] Kujawski et al: Compassionate use of remdesivir in	NCT04323761 NCT04302766 NCT04315948 NCT04252664 NCT04257656

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Drug	Proposed mechanism of action		Evidence for SARS-CoV-2	Clinical trials[7]
			three of the first 12 cases of COVID-19 in the United States.[25] Grein et al: Compassionate use of remdesivir in severe COVID-19 led to improvement in oxygen status in 36 of 53 (67.9%) of patients. The study is limited by absence of control arm.[26]	NCT04292899 NCT04292730
IL-6 inhibitors	Curbs cytokine release syndrome by inhibiting IL-6 receptors	Clinical	Xu et al: Defervescence and reduction in supplemental oxygen requirement in 21 patients after tocilizumab use.[27]	NCT04315298 NCT04320615 NCT04317092 NCT04306705 NCT04322188
Anti—GM-CSF	Reduce severity of cytokine release syndrome by inhibiting GM-CSF pathway	No clinical data available as of yet.		
Convalescent plasma	Antibody neutralization of virus	Clinical	Shen et al: Improvement in clinical status following administration of convalescent plasma in addition to antiviral agents in 5 patients with ARDS due to COVID-19.[28]	NCT04323800 NCT04292340 NCT04264858

[a]ACE2 = angiotensin-converting enzyme; ARDS = acute respiratory distress syndrome; COVID-19 = coronavirus disease 2019; CYP3A4 = cytochrome P450 3A4; EC_{50} = half-maximal effective concentration; GM-CSF = granulocyte-macrophage colony-stimulating factor; Il-6 = interleukin 6; LPV/r = lopinavir/ritonavir; PCR = polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

STRATEGIES DIRECTED AGAINST THE VIRUS

Chloroquine and Hydroxychloroquine

Chloroquine is an aminoquinoline antimalarial drug discovered in 1934.[29] In addition to antimalarial activity, it has antiviral, anti-inflammatory, and immunomodulatory effects. These properties have led to its use in inflammatory rheumatologic diseases. Various mechanisms have been proposed for its antiviral activity (Table). Chloroquine can rapidly increase the endosomal pH, thereby reducing the fusion between SARS-CoV-2 and the endosome. By impairing terminal glycosylation of angiotensin-converting enzyme 2 (ACE2), it decreases the affinity of SARS-CoV-2 with ACE2, which serves as its main entry point into the cell.

Chloroquine's antiviral activity has been tested against SARS-CoV, MERS-CoV, human immunodeficiency virus (HIV), dengue, and chikungunya.[29-31] However, it failed to show any benefit in clinical or animal models.[32] Paton et al[33] tested chloroquine as a prophylactic agent against influenza. In this randomized double-blind placebo-controlled trial, chloroquine failed to prevent influenza infection. Similarly, after showing a promising in vitro effect, chloroquine failed to reduce the duration of dengue viremia and nonstructural protein 1 antigenemia.[34] Moreover, chloroquine did not improve acute disease and was associated with more chronic arthralgia in patients with chikungunya infection.[35,36]

Assessing its activity against SARS-CoV-2, Wang et al[8] showed, in in vitro studies on Vero cells, that chloroquine affected the entry and post-entry stages of infection. They suggested that a daily dose of 500 mg of chloroquine would achieve the half-maximal effective concentration (EC_{50}) in clinical scenarios. Subsequently, Gao et al[11] reported their preliminary finding on the use of chloroquine in 100 patients in Wuhan, China, which concluded that chloroquine prevented exacerbation of
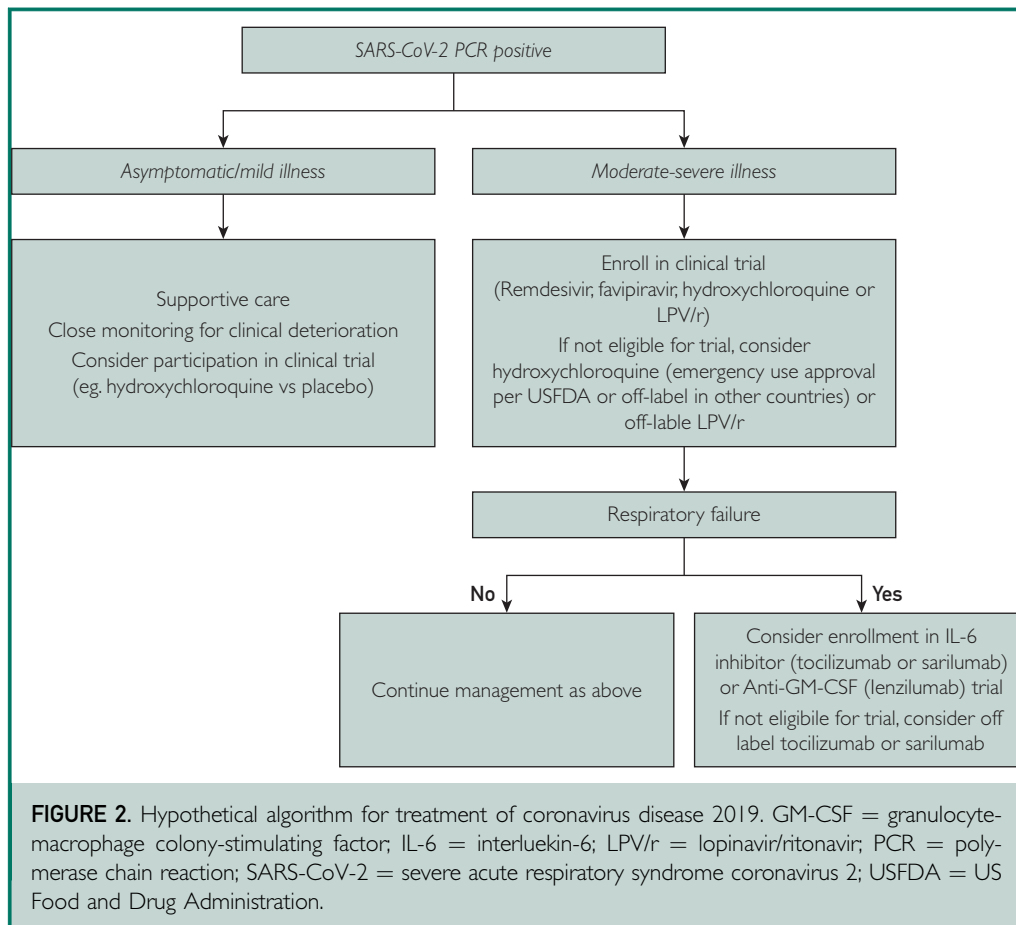
pneumonia, improved findings on lung imaging, and shortened the course of the disease. However, the full, peer-reviewed publication of this clinical trial is not available.

Because of a shortage of chloroquine and a superior safety profile, hydroxychloroquine has been proposed as an alternative for the treatment of COVID-19. Yao et al[9] compared the EC_{50} for hydroxychloroquine and chloroquine and found that hydroxychloroquine was more potent (EC_{50} of 0.72 μM) than chloroquine (EC_{50} of 5.47 μM). However, in a subsequent analysis, Liu et al[10] found chloroquine to show a lower EC_{50} across four different multiplicities of infection. The antiviral effects of hydroxychloroquine were tested in a small open-label non-randomized trial by Gautret et al.[12] In this study, viral eradication was faster in the hydroxychloroquine group compared with the untreated control group; this finding was further magnified in six patients who received azithromycin for prevention of bacterial infection. However, there are major limitations of the study that raise caution in the interpretation of the results. Indeed, the International Society of Antimicrobial Chemotherapy released a statement that the study does not meet the Society's expected standards.[37] Only 20 of 26 patients treated with hydroxychloroquine were included in the final analysis. The SARS-CoV-2 polymerase chain reaction (PCR) cycle threshold (which is inversely related to the viral load) was higher in patients treated with hydroxychloroquine and azithromycin combination (therefore, they have lower viral load and expected to clear sooner). The majority of the patients treated with hydroxychloroquine had milder disease (only 22% patients had lower respiratory tract infection). The comparator group was from a different hospital that may have different clinical practices.[38] A follow-up to this study by the same investigators reported the promising clinical and virologic outcomes of 80 patients managed with the combination of hydroxychloroquine and azithromycin. Although the authors confirmed the efficacy of this combination

therapy, this single-arm observational report lacks an all-important control group, thereby limiting the strength of their conclusion.[13] Molina et al[14] also investigated the use of hydroxychloroquine and azithromycin and reported that 8 of 10 (80.0%) patients remain positive for SARS-CoV-2 PCR on days 5 to 6 after treatment initiation. In another study that is yet to be peer-reviewed, clinical improvement was observed in 25 of 31 (80.6%) of patients treated with hydroxychloroquine as compared to 17 of 31 (54.8%) in the control group that received standard treatment (including antivirals other than hydroxychloroquine).[15] Collectively, the suggestion of clinical benefit for the use of chloroquine and hydroxychloroquine for SARS-CoV-2 should be interpreted with caution, as it is supported only by limited, and often times conflicting, clinical data. Accordingly, the use of chloroquine or hydroxychloroquine for COVID-19 should be under clinical trials or treatment registries, and their off-label use outside of these trials is not currently recommended.

Before starting hydroxychloroquine or chloroquine, patients should have corrected QT measured.[39] Certain patient groups must be tested for glucose-6-phosphate dehydrogenase deficiency, which is associated with hemolytic anemia with chloroquine use. Although chloroquine and hydroxychloroquine are considered safe, the therapeutic index for chloroquine is narrow, and it has been associated with gastrointestinal symptoms, retinopathy, and deafness/tinnitus, as well as life-threatening toxicity, including cardiomyopathy and arrhythmias and methemoglobinemia.[40,41]

Several clinical trials are underway to provide real-world clinical data on the efficacy of chloroquine and hydroxychloroquine for the treatment of COVID-19 (Supplemental Table).[11] Based on current limited data, strong recommendations for widespread off-label clinical use cannot be made. However, the US Food and Drug Administration (FDA) has issued an emergency-use authorization of chloroquine and hydroxychloroquine to treat hospitalized patients with COVID-19.[42]

FIGURE 2. Hypothetical algorithm for treatment of coronavirus disease 2019. GM-CSF = granulocyte-macrophage colony-stimulating factor; IL-6 = interluekin-6; LPV/r = lopinavir/ritonavir; PCR = polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; USFDA = US Food and Drug Administration.

Clinicians considering the use of these agents are advised to enroll their patients in clinical trials. In the event that trial participation is not possible, careful consideration of the risks versus potential benefits is emphasized. Detailed information on these clinical trials is available in the Supplemental Table (available online at http://www.mayoclinicproceedings.org) and on clinicaltrials.gov.[7]

Favipiravir

Favipiravir is a non-nucleoside RNA polymerase inhibitor that was developed for the treatment of influenza. It has also been tested against Ebola, Marburg, Nipah, Lassa fever, and Zika viruses.[43-45] Favipiravir was used alone or in combination with monoclonal antibodies as post-exposure prophylaxis for Ebola in at least five health care workers.[46] Its use, in combination with ribavirin, potentiated its effect in vitro.[45,47]

There are limited published studies regarding in vitro and clinical data on the use of favipiravir in coronavirus infections. In a study that was previously shared before peer-review but has since been temporarily removed, favipiravir and lopinavir/ritonavir (LPV/r) were compared in an open-label study of 80 patients during the current SARS-CoV-2 pandemic in China.[16] When compared with LPV/r, favipiravir was associated with shorter time-to-viral-clearance (median 4 versus 11 days, $P<.001$) and significant improvement in chest imaging (improvement rate 91.43% versus 62.22%, $P=.004$). Additionally, the Japanese Health Ministry commented that the use of favipiravir in 70 to 80 patients did not produce similar clinical benefit.[48] These contrasting findings call for a randomized controlled trial to assess the safety and efficacy of favipiravir for the treatment of COVID-19 (Table).

Lopinavir/Ritonavir

Lopinavir (LPV) is a protease inhibitor approved for use, in a fixed-dose combination with ritonavir, as part of antiretroviral therapy for HIV infection. LPV/r was used for the treatment of SARS-CoV during the 2003 outbreak. Chu et al[49] showed the cytopathic effect of LPV/r on SARS-CoV by in vitro antiviral susceptibility testing, although it showed weak antiviral activity. In a subsequent study of 41 patients who received LPV/r or standard of care, there was a significant difference in the incidence of ARDS or mortality at day 21 (LPV/r = 2.4% versus control = 28.8%, $P<.001$). A multivariate analysis showed that lack of LPV/r use was independently associated with worse outcomes. Notably, ribavirin was used concurrently with LPV/r because of its known broad-spectrum antiviral activity and possibly an indirect immunomodulatory effect.[50] During the 2003 SARS outbreak, Chan et al[51] expanded the study to 75 patients treated with LPV/r and compared those with matched controls. All patients also received steroids and ribavirin. In the initial-therapy group of 44 patients, LPV/r was initiated within a median of 5.5 days. When compared with controls (n=634), there was significant decrease in mortality (2.3% versus 15.6%, $P<.05$), intubation rate (0% versus 11%, $P<.05$), and the proportion requiring methylprednisolone rescue (27.3% versus 55.4%, $P<.05$). However, in the rescue-therapy group of 31 patients, LPV/r was administered at a median of 18 days after symptom onset (when patients had been off ribavirin). No statistical difference was seen between LPV/r and the control group (n=343) in mortality, intubation rate, and steroid use. These observations suggest that the efficacy of LPV/r may be best achieved when it is given early in the course of coronavirus infection. The MERS outbreak reignited interest in the anti-coronavirus activity of LPV/r. In vitro data and animal model showed therapeutic potential in human MERS infection.[52-54] A clinical trial, MERS-CoV Infection Treated With a Combination of Lopinavir/Ritonavir

and Interferon Beta-1b, (MIRACLE) is ongoing to evaluate the efficacy of LPV/r in combination with interferon beta (IFN-β).[55]

Because of anecdotal clinical data from the previous coronavirus outbreaks, LPV/r has been used for the SARS-CoV-2 outbreak in China and has been part of the Chinese national guidelines.[56] Reports of use in individual cases or series are available; however, it is difficult to critically appraise the data because of concomitant use of Chinese herbal and other therapies.[17-21] In a retrospective cohort study, Deng et al[23] has shown that combination of arbidol with LPV/r was significantly better than LPV/r alone for nasopharyngeal swab PCR conversion to negative after 7 d (75% versus 35%, $P<.05$), after 14 d (94% versus 52.9%, $P<.05$), and improvement on computed tomography scan of the chest (69% versus 29%, $P<.05$).[23] However, in a randomized controlled open-label study, LPV/r combination was not significantly better than the standard of care for the management of severe COVID-19.[22] This randomized controlled trial has some noteworthy limitations. First, the mortality rate was high, which suggests the enrollment of patients with severe COVID-19. Second, the median time from symptom onset to randomization was 13 days, which suggests that the drug may have been administered too late, when viral replication may no longer be the major factor. A total of 42% of patients remained positive at day 28, raising the concern about its antiviral efficacy. An absolute difference of 6.8% in 28-day mortality was observed, but this did not reach statistical significance. Collectively, the data on the use of LPV/r for the treatment of COVID-19 is very limited. Larger controlled clinical studies are needed to evaluate the role of LPV/r (potentially in combination with ribavirin) in COVID-19 (Table).

Remdesivir

Remdesivir is an investigational nucleoside analog that works as an RNA-chain terminator by inhibiting RNA-dependent viral RNA polymerase. It is a monophosphoramidate prodrug

of adenosine C-nucleoside,[57] and its structure is similar to tenofovir alafenamide, which is active against HIV and hepatitis B virus.[58] It was developed by Gilead Sciences (Foster City, CA) for treatment of Ebola during the 2013−2016 outbreak. The use of remdesivir in the rhesus monkey model showed that once-daily intravenous administration resulted in suppression of Ebola viral replication and protected animals from lethal disease.[59] Subsequently, it was used in two clinical cases (in combination with other therapies) with a successful outcome.[60,61] However, a randomized controlled trial in patients with Ebola showed that remdesivir-treated patients had higher mortality compared with three monoclonal antibodies (53.1% versus 33.5%, 35.1%, and 49.7%, respectively).[62]

Remdesivir was shown to have in vitro activity against SARS-CoV and MERS-CoV.[57,63-65] Sheehan et al[54] showed that remdesivir, when combined with IFN-β had superior antiviral properties as compared with LPV/r-IFN-β.[54] Accordingly, there has been renewed interest in remdesivir for treatment of SARS-CoV-2, especially after early anecdotal use in China suggested that it may offer benefit. However, peer-reviewed clinical data for remdesivir use in COVID-19 is still not available. In vitro data shows that remdesivir has potent activity against SARS-CoV-2—infected Vero cells.[8] Remdesivir had higher selectivity index (ratio of half-cytotoxic concentration [CC_{50}] and EC_{50}) when compared with ribavirin, penciclovir, favipiravir, nafamostat, and nitazoxanide ($>$129.87 and $>$88.50 versus $>$3.65, $>$4.17, $>$6.46, $>$4.44, and $>$16.76, respectively). Holshue et al[24] reported the first successful use of remdesivir, given on a compassionate basis, in a 35-year-old US man with COVID-19. Kujawski et al[25] further reported that 3 of the first 12 cases of COVID-19 in the United States received compassionate-use remdesivir as treatment. The three patients received remdesivir for 4 to 10 days, which resulted in improvement in respiratory symptoms. All three patients had gastrointestinal symptoms and elevation of serum transaminases. Lescure et al[66] reported the outcomes of

the first five cases of COVID-19 in Europe, including three who received remdesivir. One of these three, a 31-year-old patient, discontinued remdesivir on day 5 of therapy due to elevated alanine aminotransferase, but recovered. A second, 48-year-old patient, received 10 days of therapy and recovered; and a third, an 80-year-old patient, received 10 days of therapy but died on day 24.

The study of 53 patients who received compassionate remdesivir for severe COVID-19 showed improvement in the oxygen status of 36 (68%) patients.[26] The reported mortality rate was 13%, which is lower than the anticipated mortality rate of severe COVID-19, albeit the variability in supportive care and available resources could also account for the difference in mortality. Moreover, the results of this cohort study are limited by the lack of a control group, the exclusion of eight (13%) patients from the final analysis, and a relatively small sample size. There are several ongoing and expanding randomized controlled trials to evaluate the safety and antiviral activity in patients with COVID-19. Currently, the use of remdesivir is restricted to controlled clinical trials, although it is also available through an expanded-access program and a compassionate-use program for individuals who are not eligible to participate in controlled clinical trials. Only results of these controlled clinical trials will provide the data on its true efficacy and safety.

Based on in vitro data, it is known that remdesivir has wide therapeutic index, high genetic barrier to resistance, and long intracellular half-life.[38,58,59] Remdesivir is also highly selective for viral polymerases and has a low propensity for human toxicity. Gilead has now stopped supplying remdesivir for compassionate use in adults but has opened an expanded access program. Most of its drug supply is now reserved for patients enrolled in several ongoing randomized controlled trials. The dose in clinical trials is 200 mg intravenously on day 1 followed by 100 mg intravenously daily for a total of a 5- or 10-day course (Table).

Other Candidate Drugs

Several compounds that are also being proposed, but with much more limited experimental or clinical data, are nitazoxanide (an antiparasitic drug with broad-spectrum antiviral activity), ribavirin (a broad-spectrum antiviral drug), baloxavir (an anti-influenza drug that is undergoing clinical trials in China), among many others. Data on these drugs are scant and very limited and will not be discussed further in this review.

IMMUNOMODULATION: STRATEGIES DIRECTED AGAINST INFLAMMATORY CYTOKINE STORM

A pro-inflammatory stage of COVID-19 that often presents later in the course of infection is believed to be mediated by cytokines, including granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin 6 (IL-6). This is clinically manifested by the development of severe pneumonia leading to ARDS and the requirement for mechanical ventilation.[67] This pro-inflammatory storm is associated with a high risk of multiorgan failure and mortality. Accordingly, there has been an interest in the use of pharmacologic compounds directed against these cytokines.

Anti−GM-CSF

GM-CSF is believed to be a key cytokine mediator of the pro-inflammatory state in patients with COVID-19. Although there has been no clinical data on its use in patients with COVID-19, mechanistically, blocking the GM-CSF pathway is expected to reduce the severity of cytokine-induced inflammation. Based on this, a randomized controlled clinical trial is planned to assess the efficacy and safety of lenzilumab, a humaneered recombinant monoclonal antibody against GM-CSF. Lenzilumab has undergone phase I and II studies when it was assessed for the treatment of cytokine release syndrome associated with chimeric antigen receptor T cell (CAR-T cell) therapy. Riovant Sciences (Basel, Switzerland) also announced that they developed an anti−GM-CSF monoclonal antibody

(gimsilumab) to treat COVID-19 patients with ARDS. Gimsilumab has been tested in a phase I study of healthy volunteers (results unpublished). Binding of the monoclonal antibody to GM-CSF receptor will block the signaling pathway that leads to cytokine release syndrome, which is also believed to characterize the pro-inflammatory stage of COVID-19.

IL-6 Inhibitors

Severe COVID-19 patients are characterized by a higher baseline IL-6 level compared with nonsevere infections.[68] In critically ill patients with COVID-19, IL-6 levels were almost 10-fold higher.[69] Higher IL-6 level is closely associated with SARS-CoV-2 RNAaemia.[69] Although it is not clear whether elevation in IL-6 has a causal association with pro-inflammatory damage of the lungs or is just a consequence of the lung infection, attempts at blocking IL-6 by using monoclonal antibodies directed against IL-6 receptors have garnered interested as a potential therapeutic option.

Tocilizumab is a humanized monoclonal antibody that is used to manage cytokine release syndrome associated with CAR-T cell therapy. Sarilumab is a human immunoglobulin G1 (IgG1) monoclonal antibody approved for the treatment of rheumatoid arthritis. These IL-6 blockers bind to soluble and membrane-bound IL-6 receptors. A clinical trial involving sarilumab for the treatment of severe COVID-19 is ongoing, where the efficacy and safety of sarilumab 200-mg and 400-mg doses administered intravenously over 1 hour are being compared with standard of care (Table). Because measurement of IL-6 levels is not readily available in most institutions, C-reactive protein (CRP) levels may be used as surrogate markers of the increased pro-inflammatory state. IL-6 inhibitors rapidly decrease CRP levels after administration; therefore, CRP levels may be used to monitor the response to therapy.

During the current COVID-19 outbreak, a cohort of 21 febrile patients (including 17 severe and 4 critical patients) received tocilizumab (including 3 patients who

received a second dose), and this led to defervescence, reduction in supplemental oxygenation, and improvement in clinical symptoms. However, the absence of a control group cautions against the optimistic interpretation of this promising data. It is unclear if the patients would have improved otherwise with aggressive standard of care, even if they had not received tocilizumab.[27] Clinical trials are underway to evaluate the efficacy and safety of sarilumab and tocilizumab for IL-6 inhibition in the management of COVID-19 (Table).

Blocking IL-6 receptors may curb fever and inflammation, but this approach also blunts the host defense against infection. IL-6 inhibition is associated with increased risk of infections, albeit this is more common after chronic use and in combination with other immunosuppressive drugs. Ongoing clinical trials are excluding patients with active or untreated tuberculosis and systemic bacterial and fungal infections.

CONVALESCENT PLASMA AND NEUTRAL-IZING ANTIBODIES

The US FDA has approved the emergency investigational use of convalescent plasma for the treatment of critically ill patients with COVID-19.[70] Convalescent plasma is collected from COVID-19—recovered individuals who are eligible for blood donation. The traditional screening protocol for blood donation should be satisfied. In addition, the plasma should be collected from people with a prior confirmed diagnosis of COVID-19 who have resolved their symptoms at least 14 days before donation. In addition, they should have negative PCR for SARS-CoV-2 and high SARS-CoV-2 neutralizing antibody titers. Takeda Pharmaceuticals (Tokyo, Japan) is also developing an anti—SARS-CoV-2 polyclonal hyperimmune globulin (TAK-888).

The use of convalescent plasma resulted in a shorter hospital stay and reduced mortality in SARS[71] and H1N1 influenza.[72] It has also been used during Ebola and MERS outbreaks.[73] A preliminary report of a series of five patients with severe COVID-19 pneumonia complicated by ARDS showed that administration of convalescent plasma containing neutralizing antibody (SARS-CoV-2 IgG titers greater than 1:1000 by enzyme-linked immunosorbent assay and neutralizing antibody titer >40) led to clinical improvement.[28] There was a normalization of body temperature in four patients within 3 days, the sequential organ failure assessment score decreased, and viral load declined to negativity by day 12. ARDS resolved within 12 days in four patients. These preliminary findings are promising, but the small number and the uncontrolled nature of this study calls for further evaluation of this treatment modality in randomized controlled clinical trials. Several groups, including investigators from our institution and other academic institutions, are collaborating to achieve a common goal of developing convalescent plasma as a viable treatment of critically ill patients with COVID-19.

CONCLUSION

To date, there is no proven effective drug or immunomodulator therapy for the management of COVID-19. As this SARS-CoV-2 pandemic escalates, the search for an effective treatment regimen is at the forefront of clinical medicine and research.

Two major approaches are being actively pursued. First, strategies directed against the virus have led to the use of repurposed drugs (such as chloroquine, hydroxychloroquine, LPV/r, and ribavirin) and novel investigational compounds (such as favipiravir and remdesivir). We do not yet know which, if any, of these compounds will eventually be proven effective against SARS-COV-2. Thus, the collaboration of the health care community to engage patients for participation in clinical trials is essential. In addition to the single-center and multicenter trials, the World Health Organization recently embarked on a large mega-trial that will compare the clinical outcome of patients treated with chloroquine or hydroxychloroquine, LPV/r, and remdesivir. Second, there are numerous clinical trials that are aimed to determine if curbing the pro-inflammatory state produced during

COVID-19 with drugs such as IL-6 inhibitors (eg, sarilumab or tocilizumab) or anti—GM-CSF compounds (eg, lenzilumab and gimsilumab) will lead to better clinical outcomes by preventing or reversing ARDS and multiorgan failure.

In addition, convalescent plasma and neutralizing antibodies are being pursued for treatment (and maybe prevention). Vaccine development (which is outside the scope of this review) is also given the utmost priority. The world is eagerly awaiting the outcomes of these clinical trials, as they will inform and guide the medical community with the best evidence to fight this pandemic. The authors strongly encourage health care providers to use these off-label and experimental therapies under the direction of clinical trials and treatment registries. Until the results of these properly conducted studies are available, there is no drug that is considered to be of proven clinical benefit for the treatment of COVID-19.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **ACE2** = angiotensin-converting enzyme 2; **ARDS** = acute respiratory distress syndrome; **CC** = 50% cytotoxic concentration; **COVID-19** = coronavirus disease 2019; **CRP** = C-reactive protein; **EC$_{50}$** = half-maximal effective concentration; **FDA** = US Food and Drug Administration; **GM-CSF** = granulocyte-macrophage colony-stimulating factor; **HIV** = human immunodeficiency viruses; **IFN-α** = interferon-alpha; **IFN-β** = interferon-beta; **IL-6** = interleukin 6; **LPV** = lopinavir; **LPV/r** = lopinavir/ritonavir; **MERS-CoV** = Middle East respiratory syndrome—related coronavirus; **SARS** = severe acute respiratory syndrome; **SARS-CoV** = severe acute respiratory syndrome coronavirus; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus 2

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