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REVIEW ARTICLE

Coronavirus Disease 2019 Treatment: A Review of Early and Emerging Options

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19), has spread across the globe resulting in a pandemic. At the time of this review, COVID-19 has been diagnosed in more than 200 000 patients and associated with over 8000 deaths (Centers for Disease Control and Prevention, World Health Organization).

On behalf of the Society of Infectious Diseases Pharmacists, we herein summarize the current evidence as of March 18, 2020 to provide guidance on potential COVID-19 treatment options. It is important to caution readers that new data emerges daily regarding clinical characteristics, treatment options, and outcomes for COVID-19. Optimized supportive care remains the mainstay of therapy, and the clinical efficacy for the subsequent agents is still under investigation.

Antimicrobial stewardship programs, including infectious diseases pharmacists and physicians, are at the forefront of COVID-19 emergency preparedness.

We encourage all readers to continue to assess clinical data as it emerges and share their experience within our community in a well-controlled, adequately powered fashion.

Keywords. lopinavir/ritonavir; COVID-19; hydroxychloroquine; remdesivir; SARS-CoV-2.

In December 2019, several patients in Wuhan, Hubei, China were diagnosed with pneumonia secondary to an unknown virus. In response, an epidemiological alert was placed with the World Health Organization (WHO) dated December 31, 2019. By January 7, 2020 Chinese scientists had isolated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. In the months that followed, SARS-CoV-2, the cause of coronavirus disease 2019 (COVID-19), spread across the globe resulting in the current pandemic. At the time of this review, COVID-19 has been diagnosed in more than 245 000 patients and associated with over 10 000 deaths (Centers for Disease Control and Prevention [CDC], WHO).

On behalf of the Society of Infectious Diseases Pharmacists, we herein summarize the current evidence as of March 19, 2020 to provide guidance on potential COVID-19 treatment options. It is important to caution readers that new data emerges approximately every hour regarding clinical characteristics, treatment options, and outcomes for COVID-19. Optimized supportive care remains the mainstay of therapy, and the clinical efficacy for the subsequent agents is still under investigation. Most existing preclinical and clinical data on antiviral therapy are derived from other viruses, including SARS-CoV-1 (first reported in 2003), Middle East respiratory syndrome coronavirus ([MERS-CoV] first reported in 2012), and non-coronaviruses (eg, Ebola virus disease). It is unclear how well these data can be extrapolated to SARS-CoV-2. Furthermore, the clinical relevance of antiviral in vitro activity (defined as half-maximal effective concentration [EC_{50}] values) remains unclear given an absence of pharmacokinetic/pharmacodynamic or clinical data that equates achievable exposures relative to these values to a treatment effect. Finally, in vitro data should be compared cautiously across studies given the potential variability in testing methodologies that could impact perceived activity.

Antimicrobial stewardship programs, including infectious diseases pharmacists and physicians, are at the forefront of COVID-19 emergency preparedness [2]. We encourage all readers to continue to assess clinical data as it emerges and share their experience within our community, preferentially evaluating these agents in the context of randomized, controlled trials.

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PHARMACOLOGICAL TREATMENTS WITH POTENTIAL CLINICAL BENEFIT

Remdesivir

Remdesivir (GS-5734) is an investigational monophosphoramidate prodrug of an adenosine analog that was developed by

Gilead Sciences, Inc. in response to the Ebola outbreak in West Africa from 2014 to 2016. In its active triphosphate nucleoside form, remdesivir binds to ribonucleic acid (RNA)-dependent RNA polymerase and acts as an RNA-chain terminator. It displays potent in vitro activity against SARS-CoV-2 with an EC_{50} at 48 hours of 0.77 μM in Vero E6 cells [3]. Similar activity has been demonstrated against other zoonotic coronaviruses with EC_{50} values of 0.07 μM demonstrated for both SARS-CoV-1 and MERS-CoV [3–6]. Remdesivir is highly selective for viral polymerases and is therefore expected to have a low propensity to cause human toxicity. Accordingly, Sheahan et al [6] demonstrated a wide therapeutic index for remdesivir in a human airway epithelial cell model. The drug also displays a high genetic barrier to resistance in coronaviruses and has a long intracellular half-life that allows for once-daily dosing [7, 8]. The dose under investigation for treatment of COVID-19 is 200 mg intravenously (IV) on day 1 followed by 100 mg IV daily for up to 10 days, infused over 30–60 minutes (Table 1).

The therapeutic efficacy of remdesivir was first described in an animal model against Ebola among infected rhesus monkeys in which once-daily dosing resulted in suppression of viral replication and protection from lethal disease [9]. However, in a human study, remdesivir-treated patients with Ebola experienced a 28-day mortality rate of 53% in a randomized controlled trial of 4 experimental therapies conducted in response to the Democratic Republic of Congo outbreak of 2018, resulting in early termination of this study arm [10]. It is worth noting that this trial did not have an active control arm, and mortality rates for the other experimental treatments were 49.7% (ZMapp), 35.1% (Mab114), and 33.5% (REGN-EB3). Against MERS-CoV, Sheahan et al [5] evaluated the therapeutic efficacy of remdesivir among infected mice and found treatment significantly reduced virus lung titers, weight loss, lung hemorrhage, and lung injury scores. The authors proposed the importance of early therapy initiation to diminish virus replication and promote pulmonary repair because remdesivir demonstrated less clinical benefit with high-titer virus inoculum. Most notably, the authors also noted that prophylactic remdesivir diminished MERS-CoV replication and disease, which was similar to their findings in a murine model with SARS-CoV-1 [5, 6].

The first report of a remdesivir-treated patient with COVID-19 in the United States was a 35-year-old male in Snohomish County, Washington who received treatment on hospital day 7 (illness day 11) due to developing pneumonia and persistent fevers [11]. The patient experienced clinical improvement and negativity of oropharyngeal swab on hospital day 8, although nasopharyngeal swab remained positive. No adverse events to remdesivir were reported for the patient, which is consistent with previous case reports of use in other viruses [12, 13]. Among the first 12 patients confirmed by the CDC to have COVID-19 in the United States, 3 were treated with remdesivir via compassionate use protocol [14]. All patients reported

Table 1. Summary of Remdesivir Clinical Trials Currently Enrolling Patients in the United States as of March 18th

Identifier	Population, Design	Inclusion/Exclusion	Primary Outcome
NCT04302766	Expanded access protocol for Department of Defense-affiliated personnel with COVID-19 diagnosis	Not available	Not available
NCT04292899	Phase 3, randomized trial of 5 versus 10 days of remdesivir for treatment of severe COVID-19 Target enrollment: 400 participants	Inclusion: Adults, PCR positive ≤4 days before randomization (severe disease), oral temperature ≥37.2°C, SpO_2 ≤94% on room air, radiographic evidence of pulmonary infiltrates Exclusion: Receipt of concurrent antiviral <24 hours before study drug initiation[a], multiorgan failure, mechanical ventilator support at screening, creatine clearance <50 mL/min, ALT or AST 5 × ULN	Proportion of patients with normalization of fever and oxygen saturation through day 14
NCT04292730	Phase 3, randomized trial of remdesivir for 5 or 10 days compared with standard of care for treatment of moderate COVID-19 Target enrollment: 600 participants	Same as NCT04292899 except this study is for patients with moderate disease	Proportion of patients discharged by day 14
NCT04280705	Adaptive, randomized, placebo-controlled trial of 394 patients at 50 sites globally for up to 10 days (all sites have been recruited)	Inclusion: Adult (must agree to use contraception if of childbearing age for study duration), PCR positive <72 hours before randomization, illness of any duration and at least one of the following: radiographic infiltrates by imaging, clinical assessment, and SpO_2 ≤94% on room air, requiring mechanical ventilation and/or supplemental oxygen Exclusion: ALT or AST 5 × ULN, eGFR <30 mL/min, pregnancy or breast feeding, anticipated transfer to nonstudy site within 72 hours, allergy to study medication	Percentage of subjects reporting each severity rating by day 15 (death, hospitalized/ventilated or ECMO, hospitalized/HFNC, hospitalized/on O_2, hospitalized/not on O_2, not hospitalized/limited activity, not hospitalized/no limitations)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate transaminase; °C, degrees Celsius; COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; HFNC, high flow nasal cannula; O_2, oxygen; PCR, polymerase chain reaction; SpO_2, peripheral capillary oxygen saturation; ULN, upper limit of normal.

[a]It is currently unclear what this means with regards to repurposed drugs; however, study protocols use lopinavir/ritonavir as an example of "antiviral therapy."

transient gastrointestinal symptoms and aminotransferase elevation. All patients are reportedly recovering, but the authors were unable to assess the efficacy or safety of remdesivir based on the lack of comparator and confounding treatments, including concomitant use of corticosteroids in one patient.

There are 4 clinical trials currently enrolling patients in the United States (Table 1). Two additional trials recruiting only in China have been registered on ClinicalTrials.gov NCT04257656 (severe disease) and NCT04252664 (mild/moderate disease). Remdesivir may also be obtained through compassionate use and the emergency Investigational New Drug (eIND) application process. At the time of this review, requests for compassionate use must be submitted online via https://rdvcu.gilead.com/. Compassionate use is only considered for hospitalized patients with polymerase chain reaction (PCR)-confirmed SARS-CoV-2 requiring mechanical ventilation in whom enrollment in a clinical trial is not feasible. Patients are excluded from the compassionate use program if they do not meet the above criteria, have evidence of multiorgan failure, are receiving vasopressors for hypotension, have liver disease defined as alanine aminotransferase (ALT) >5 × upper limit of normal (ULN) or renal impairment defined as *creatinine clearance (*CrCl) <30 mL/min, or receiving dialysis or continuous venovenous hemofiltration. Inclusion and exclusion criteria for compassionate use may change, so applicants are encouraged to review the most up to date criteria for all potential patients. Clinicians should be cognizant that it typically takes a minimum of 72 hours for institutions to receive emergency institutional review board authorization (if required), protocol, and consent forms from Gilead, US Food and Drug Administration (FDA)-approval for the eIND, and eventual drug shipment. Clinicians should coordinate with their local information technology teams to build a medication order sentence into the electronic health record during this time. Patients may receive other antiviral therapies during the waiting period but must immediately discontinue them if they receive remdesivir for compassionate use.

It is interesting to note that the adaptive clinical trial protocol originally stated "remdesivir is a prodrug that is metabolized to its active form as a substrate of CYP-3A4". This implies the existence of a drug-drug interaction with CYP3A4 substrate inhibitors such as ritonavir or voriconazole. However, the protocol also stated "although remdesivir is a substrate for CYP2C8, CYP2D6, and CYP3A4 in vitro, coadministration with inhibitors of these CYP isoforms is unlikely to markedly increase remdesivir levels, as its metabolism is likely to be predominantly mediated by hydrolase activity." Unlike the former, the latter statement is substantiated by well described chemistry of the molecule. The National Institute of Allergy and Infectious Diseases was contacted about this discrepancy and in collaboration with Gilead, this has been corrected. There is no reason to believe that any significant drug interactions between remdesivir and CYP3A4 inhibitors or inducers are likely [8].

Emerging clinical evidence and available in vitro data suggest remdesivir is a promising agent for the treatment of COVID-19. Institutions should explore clinical trial enrollment or compassionate use remdesivir for moderate-to-severe patients. Additional clinical data are eagerly anticipated and should help further define the role of this agent in COVID-19.

Chloroquine and Hydroxychloroquine

Chloroquine, an antimalarial agent with anti-inflammatory and immunomodulatory activities, has gained significant interest as a potential therapeutic option for the management of COVID-19. In early February, Wang et al [3] demonstrated potent in vitro activity of chloroquine against SARS-CoV-2 with an EC_{50} at 48 hours of 1.13 μM in Vero E6 cells. These data were consistent with previous data for chloroquine's inhibitory activity against SARS-CoV-1 and MERS-CoV in various cell lines, where EC_{50} values of 1–8.8 and 3.0 μM were demonstrated, respectively [15]. These findings have supported the clinical use of chloroquine, at a dose of 500 mg by mouth twice daily, in numerous clinical trials in China during this outbreak. Although the rationale for this dosing regimen remains unclear, and peer reviewed data from the trials are currently unavailable, it was announced in mid-February that promising early results have been demonstrated. Per Gao et al [16], "thus far, results from more than 100 patients have demonstrated that chloroquine phosphate is superior to the control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus-negative conversion, and shortening the disease course according to the news briefing. Severe adverse reactions to chloroquine phosphate were not noted in the aforementioned patients."

Although this development has been encouraging, supply issues in the United States and cardiovascular toxicity concerns limit the use of chloroquine. As an alternative, hydroxychloroquine, a compound that differs from chloroquine only by a single hydroxyl group, has garnered interest. Hydroxychloroquine is perceived as having better tolerability than chloroquine, which has led to long-term usage in rheumatological disorders. Historically, very limited data were published assessing the activity of hydroxychloroquine against coronaviruses. In 2006, Biot et al [17] assessed the comparative inhibitory activity of chloroquine and hydroxychloroquine against SARS-CoV-1 in Vero cells. The authors demonstrated that chloroquine had an approximately 5-fold increased potency (EC_{50} of 6.5 ± 3.2 μM) compared with that of hydroxychloroquine (EC_{50} of 34 ± 5 μM).

Against SARS-CoV-2, Yao et al [18] performed a 2-part study assessing the comparative in vitro activity of chloroquine and hydroxychloroquine and performed pharmacology-based pharmacokinetic (PBPK) modeling to assess comparative exposure

and predicted activity of these 2 compounds in the lung. In vitro analyses in Vero cells demonstrated that the potency of hydroxychloroquine (EC_{50} of 0.72 μM) was greater than that of chloroquine (EC_{50} of 5.47 μM) against SARS-CoV-2 [18].

To inform optimal dosing of hydroxychloroquine, the investigators then performed PBPK modeling. In this analysis, the investigators utilized human population pharmacokinetic and rat lung penetration data for each compound to estimate free trough concentrations in the lung to EC_{50} ratios (R_{LTEC}) [18]. Because 500 mg of chloroquine by mouth twice daily has been reported to demonstrate efficacy against SARS-CoV-2, the target R_{LTEC} for hydroxychloroquine regimens was set to ≥2.38 (day 1), 5.92 (day 3), and 18.9 (day 5), which were the R_{LTEC} values predicted with the "efficacious" 500 mg by mouth twice-daily dosing of chloroquine [16]. Various dosing regimens were simulated, but 2 are particularly notable. The first was an oral loading dose of 1200 mg (divided 800 mg then 400 mg) on day 1, followed by 400 mg daily. This regimen led to significantly higher R_{LTEC} on day 1 (33.3), day 3 (55.1), and day 5 (103) than those values demonstrated with chloroquine. The second regimen was a loading dose of 800 mg (400 mg × 2) on day 1 followed by 200 mg twice daily. This was also associated with higher R_{LTEC} values than chloroquine on day 1, 3, and 5 (corresponding to 21.0, 38.9, and 85.4, respectively) [18]. The authors concluded that these data support the lower dose regimen because R_{LTEC} values were significantly higher than those with the "proven efficacious" regimen of 500 mg of chloroquine by mouth twice daily. Clinicians should note that both chloroquine and hydroxychloroquine have half-lives of ~40 days [19], and therefore short durations would likely provide prolonged courses of therapy. This was exemplified in the PBPK modeling in which R_{LTEC} values with hydroxychloroquine were predicted to still be above the targeted efficacy threshold on day 10, even with a 5-day course of therapy.

Although these data are encouraging for the potential role of hydroxychloroquine against SARS-CoV-2, we caution against solely relying on these data to support dosing regimens for patients. The use of 500 mg of chloroquine by mouth twice daily as the reference for efficacy is rational given initial reports from China [16], but it is important to note that this dosing still requires validation, and the improved R_{LTEC} values reported are largely driven by the finding that hydroxychloroquine was 7.6 times more potent than chloroquine in vitro. Although this enhanced potency may very well prove true as more data become available, this report is counter to the relative potency demonstrated with the structurally similar SARS-CoV-1 strain in 2006 in which chloroquine was approximately 5 times more potent than hydroxychloroquine. In addition, a recently published study has demonstrated that the EC_{50} value for chloroquine is 1.13 μM [3], similar to the value reported for hydroxychloroquine in the analysis by Yao et al [18].

Because there are currently no efficacy data available for hydroxychloroquine in COVID-19, additional consideration should be given to the optimal dosing strategy. We use the following example to illustrate this point. If one were to consider these 2 compounds to be equally potent (identical EC_{50} values) and utilize the PBPK data from Yao et al [18], the 800 mg load, 400 mg daily regimen for hydroxychloroquine would yield R_{LTEC} values of 2.76, 5.11, and 11.2 on day 1, 3, and 5, respectively. These R_{LTEC} values would be slightly lower than those achieved with 500 mg by mouth twice daily of chloroquine on day 3 and significantly lower than those on day 5, suggesting the potential need for a higher dose to have similar activity. Although the 400 mg daily regimen is the most common regimen currently being assessed in clinical trials, the rationale for that dose is currently unclear, and at least 1 clinical trial in China is using a higher dose of 800 mg by mouth daily.

To this point, Gautret et al [20] recently published their initial experience on the impact of 200 mg of hydroxychloroquine by mouth every 8 hours on viral eradication in patients with COVID-19. The authors reported on 36 patients (20 hydroxychloroquine and 16 control) who were COVID-19 positive and able to have nasopharyngeal sampling for the first 6 days of therapy (in the treated arm). The investigators demonstrated that hydroxychloroquine (14 of 20, 70%) was superior to standard of care (2 of 16, 12.5%; $P = .001$) in eradicating SARS-CoV-2 from the nasopharynx. It is interesting to note that 6 patients were prescribed azithromycin "to prevent bacterial super-infection" and the investigators found that viral eradication was numerically superior in this subgroup (6 of 6, 100%) compared with those who received hydroxychloroquine alone (8 of 14, 57%). The authors concluded that azithromycin "reinforced" the SARS-CoV-2 viral load achieved by hydroxychloroquine. Although these data are intriguing, certain limitations to this data set must be acknowledged. First, although viral eradication is an important endpoint, the authors did not report clinical outcomes in these patients. Second, the cohort initially contained 26 hydroxychloroquine patients, but 6 of them were removed from the analysis due to early cessation of hydroxychloroquine therapy including 3 PCR-positive patients who were transferred to the intensive care unit (ICU), 1 PCR-negative patient who passed away, and 1 PCR-positive patient who discontinued hydroxychloroquine due to nausea. Finally, the hydroxychloroquine monotherapy arm included patients with significantly higher viral loads, represented by lower cycle threshold (C_T) values than those who received combination therapy. If the hydroxychloroquine monotherapy patients with C_T values <23 are separated from those with C_T values ≥23, there is a notable discordance in viral eradication rates (1 of 5, 20% vs 7 of 9, 78%), with this latter number approaching the 6 of 6 demonstrated with hydroxychloroquine and azithromycin combination therapy in which all patients had C_T values ≥23. Given this finding, the small numbers in

this study, the lack of clinical outcomes presented, the potential for additive toxicity with hydroxychloroquine and azithromycin, and the desperate need to practice good antimicrobial stewardship during the COVID-19 pandemic, we would caution clinicians against using these data to support combination therapy.

Despite all of the unknowns, the initial experience in China is encouraging for the potential role of chloroquine, or alternatively hydroxychloroquine, for the management of COVID-19. Clinicians are encouraged to closely follow subsequent peer-reviewed publications from the ongoing chloroquine and hydroxychloroquine trials, because others have raised concerns regarding the apparent in vitro and/or in vivo discordance witnessed with chloroquine in other viral infections [21]. Furthermore, if hydroxychloroquine is utilized, careful consideration for dose selection should be given in accordance with the aforementioned data, as well as considerations for when to initiate during the course of illness.

Lopinavir/Ritonavir

Lopinavir is a human immunodeficiency virus (HIV)-1 protease inhibitor administered in fixed-dose combination with ritonavir (LPV/r), a potent CYP3A4 inhibitor that "boosts" lopinavir concentrations. Lopinavir seems to block the main protease of SARS-CoV-1, inhibiting viral replication [22]. In 2003, Chu et al [23] evaluated a series of antivirals for in vitro activity against SARS-CoV-1. They reported lopinavir at 4 μg/mL and ribavirin at 50 μg/mL inhibited SARS-CoV-1 after 48 hours of incubation and that the agents were synergistic when used together [23]. de Wilde et al [24] later described the antiviral activity of lopinavir against SARS-CoV-1 and demonstrated an EC_{50} 17.1 ± 1 in Vero E6 cells, which is near the upper range of LPV plasma concentrations previously measured in patients with HIV [25]. Sheahan et al [5] evaluated the in vitro efficacy of LPV/r in combination with interferon beta (INFb) against MERS-CoV and found the addition of LPV/r did not significantly enhance antiviral activity of INFb alone (EC_{50} = 160 vs 175 IU/mL, respectively). They also described the EC_{50} of LPV/r (8.5 μM) and LPV alone (11.6 μM), suggesting similar activity to that described for SARS CoV-1. Despite in vitro activity against MERS-CoV, therapeutic doses of LPV/r + INFb in mice models failed to reduce virus titer and exacerbated lung disease [5]. This is notable because this was the same study in which remdesivir demonstrated both more potent in vitro activity as well as in vivo efficacy. However, the in vivo animal data for MERS-CoV appears equivocal given that a nonhuman primate model demonstrated improved clinical and pathological features after LPV/r treatment [26]. A randomized controlled trial of LPV/r and recombinant interferon-β1b versus placebo is currently enrolling for patients with MERS-CoV, which might help clarify the apparent discrepancy between in vitro and animal models [27].

Based on in vitro findings, Chu et al [23] utilized combination therapy with LPV/r, ribavirin, and corticosteroids for any newly diagnosed patient with SARS-CoV-1 without acute respiratory distress syndrome (ARDS) starting in April 2003. Patients receiving LPV/r combination therapy (N = 41) were matched to historical patients receiving ribavirin plus corticosteroids (N = 111), and a significant reduction in the development of ARDS or death at 21 days was observed (2.4% vs 28.8%, $P < .001$). This was corroborated by an expanded case-control matched study of 75 LPV/r-treated patients from the same center that demonstrated a significant reduction in pulse steroid use (27.3% vs 55.4%), intubation (0% vs 11%), and mortality (2.3% vs 15.6%) among patients who received LPV/r combination versus no LPV/r, respectively, as initial therapy [28]. More important, the benefits of LPV/r were only demonstrated in patients who received initial treatment with LPV/r (defined as initiation of drug at time of SARS-CoV-1 diagnosis). There was no observed benefit when LPV/r was added as rescue or salvage therapy (death rate 12.9% vs 14%).

This compelling mortality difference in SARS-CoV-1 and continued investigation in MERS-CoV led to inclusion of LPV/r in the Chinese SARS-CoV-2 guidelines at a dose of 400 mg/100 mg (2 capsules/tablets) by mouth twice a day for no more than 10 days even though to our knowledge, no in vitro data for LPV/r in SARS-CoV-2 exist [29]. In pediatric patients weighing 15–40 kg, the recommended dose in the United States is 10 mg/kg suspension by mouth twice daily. There are 10 ongoing registered clinical trials in China, Korea, Thailand, and Hong Kong evaluating LPV/r as monotherapy or in combination with other antivirals (eg, ribavirin, interferon beta-1b) or traditional Chinese medicine for treatment of COVID-19.

Real-world data for treatment of COVID-19 with LPV/r are emerging. Young et al [30] reported outcomes of the first 18 patients infected with SARS-CoV-2 in Singapore, 5 of whom received LPV/r monotherapy. Three patients had reduction in oxygen requirements after treatment initiation; 2 deteriorated to respiratory failure. Two of 5 patients (40%) experienced clearance of viral shedding on treatment, and 4 of 5 (80%) experienced adverse events that precluded completion of the planned 14-day treatment course. Other published case reports or case series from Korea and China comprising 6 total patients describe decreased viral load and clinical improvement after LPV/r initiation. These data are difficult to interpret in light of concomitant drug therapies, varied time points of therapy initiation, heterogeneous severity of illness amongst patients, and the lack of comparator treatments [31–33]. Finally, early reports from Wuhan have described some patients receiving LPV/r in addition to other therapies (including corticosteroids), but clinical outcomes and adverse events are either not described or not delineated by treatment group [34–36].

Most recently, Cao [37] et al reported the results of an open-label randomized trial comparing LPV/r 400/100 mg twice daily

(n = 99) to standard care (n = 100) for the treatment of COVID-19 pneumonia. The primary endpoint was defined as the time from randomization to an improvement of 2 points on a 7-category ordinal scale or discharge from the hospital. Secondary outcomes included 28-day mortality, time until discharge, and virologic response on repeat oropharyngeal swabs over the course of the study. The median time from symptom onset to randomization was 13 (interquartile range [IQR], 11–16) days, and this did not differ between the groups. There was no significant difference in time to clinical improvement (16 [IQR, 13–17] days vs 16 [IQR, 15–17] days), time from randomization until discharge (12 [IQR, 10–16] days vs 14 [IQR, 11–16] days), or mortality (19.2 % vs 25.0%; absolute difference, −5.8; 95% confidence interval [CI], −17.3% to 5.7%) between patients receiving LPV/r and standard care. When the 3 patients who died after randomization but before receiving LPV/r were removed, there remained no difference in mortality (16.7% vs 25.0%; absolute difference, −8.3 percentage points; 95% CI, −19.6 to 3.0). More important, there was no difference between treatment arms in reduction of viral loads over time between the 2 groups.

With the available data, it is difficult to assess whether LPV/r has a role for the treatment of COVID-19 either as monotherapy or in combination. The data from SARS-CoV-1 are encouraging, but this must be weighed against the inferior performance in mouse models against MERS-CoV, the less potent in vitro activity compared with remdesivir and chloroquine for SARS-CoV-1, and limited data suggesting no advantage over standard care for SARS-CoV-2. More important, it warrants comment that in the recent randomized controlled trial in COVID-19 pneumonia, the median time from symptom onset to initiation of therapy was 13 days, and in the SARS-CoV-1 experience, therapy appeared effective if started early, but not as rescue and/or salvage. If used, drug interactions must be screened, and gastrointestinal toxicities, including diarrhea, nausea, and vomiting, and hepatotoxicity, require close monitoring, particularly because elevated aspartate transaminase or ALT may exclude patients with COVID-19 from clinical trials. The LPV/r tablets can be taken without regard to food but should not be crushed because this decreases systemic exposure; solution should be used in patients who cannot receive intact tablets [38].

Nitazoxanide

Nitazoxanide has demonstrated potent in vitro activity against SARS CoV-2, with an EC_{50} at 48 hours of 2.12 μM in Vero E6 cells [3]. This potent activity is consistent with EC_{50} values for nitazoxanide and its active metabolite, tizoxanide, against MERS-CoV in LLC-MK2 cells in which EC_{50} values of 0.92 and 0.83 μM, respectively, have been demonstrated [39]. Nitazoxanide displays broad-spectrum in vitro antiviral activity against influenza, respiratory syncytial virus, parainfluenza, rotavirus, and norovirus among others in addition to coronaviruses [39]. This broad-spectrum antiviral activity is believed to be due to the fact that the mechanism of action is based on interference with host-regulated pathways involved in viral replication rather than virus-specific pathways [39].

Due to its broad-spectrum antiviral activity, nitazoxanide is being investigated for the management of influenza and other acute respiratory infections. Positive results were demonstrated in a phase 2b/3 study for the outpatient management of influenza, in which a dose of 600 mg by mouth BID of nitazoxanide was associated with a ~1-day improvement in time to resolution of symptoms when compared with placebo (P = .008) [40]. Three phase 3 randomized controlled trials in uncomplicated influenza have since been completed (ClinicalTrials.gov Identifier NCT01610245 [March 2018], NCT02612922 [April 2018], and NCT03336619 [September 2019]), although results are unavailable. Nitazoxanide failed to reduce the duration of hospitalization or the time to symptom alleviation in a phase 2 randomized controlled trial in patients with severe acute respiratory illnesses requiring hospitalization, predominantly caused by respiratory viruses [41]. Although the in vitro activity of nitazoxanide against SARS-CoV-2 is encouraging, more data are clearly needed to determine its role in the management of COVID-19.

ADJUNCTIVE PHARMACOLOGICAL TREATMENTS

Tocilizumab

Tocilizumab is a humanized monoclonal antibody that inhibits both membrane-bound and soluble interleukin-6 (IL-6) receptors. Interleukin-6, which is secreted by monocytes and macrophages, is one of the main drivers of immunologic response and symptoms in patients with cytokine-release syndrome (CRS). Although tocilizumab was first approved by the FDA in 2010 for the treatment of rheumatoid arthritis, it has gained traction in recent years for treatment of patients with CRS following chimeric antigen receptor T-cell (CAR T) therapy as a corticosteroid-sparing agent [42]. Indeed, it received FDA approval for severe or life-threatening CAR T-associated CRS in 2017 due to its efficacy and safety profile. Although criteria for grading CRS severity varies by cancer center, it has been proposed to administer tocilizumab to CRS patients with any of the following: oxygen requirement <40%, hypotension responsive to fluids or a low dose of a single vasoactive agent, or Grade 2 organ toxicity as defined by the Common Terminology Criteria for Adverse Events [43]. Interleukin-6 antagonism may make a patient more susceptible to bacterial infection and has been associated with neutropenia and thrombocytopenia in patients receiving chronic therapy with tocilizumab for giant cell arteritis or rheumatoid arthritis. In a case series of 53 adult patients with relapsed or refractory B-cell acute lymphoblastic leukemia, Grade 3 CRS or higher was associated with increased risk of subsequent infection, but it was unclear whether tocilizumab

or corticosteroid use promoted this risk [44]. There were no reported adverse events in the 60 tocilizumab-treated patients submitted to the FDA for the CRS indication, which recommends a maximum of 4 doses for treatment [45].

Hyperinflammatory states and cytokine storming, including elevated IL-6, has been reported in severe COVID-19 and were associated with increased mortality in patients in China [36]. A preprint (nonpeer reviewed) case series of 21 patients treated with tocilizumab between February 5 and 14, 2020 in China reported marked success, including rapid resolution of fever and C-reactive protein, decreased oxygen requirements, and resolution of lung opacities on computerized tomography imaging [46]. The authors state the patients all had "routine treatment for a week" before tocilizumab, which was described as "standard care according to national treatment guidelines" including lopinavir, methylprednisolone, and other supportive care. All patients had IL-6 analyzed before tocilizumab administration with a mean value of 132.38 ± 278.54 pg/mL (normal <7 pg/mL). It should be noted that in the United States, IL-6 monitoring is a send-out laboratory for most institutions with a turnaround time of 3–7 days. No adverse events were described in the Chinese cohort; however, long-term assessment was not done.

Immunotherapy with tocilizumab is listed as a treatment option for severe or critical cases of COVID-19 with elevated IL-6 in the 7th edition of the National Health Commission of the People's Republic of China COVID-19 Diagnosis and Treatment Guide [29]. The recommended dose is 4–8 mg/kg or 400 mg standard dose IV once, with the option to repeat a dose in 12 hours (not to exceed a total dose of 800 mg). There are 2 ongoing trials in China evaluating safety and efficacy of tocilizumab for patients with COVID-19 pneumonia, but none registered in the United States.

We anticipate that more data regarding tocilizumab use in patients with COVID-19 will emerge, and it will be imperative for clinicians to evaluate it closely. The optimal timing of tocilizumab administration during the disease course is not yet defined, nor is there a known IL-6 threshold for progression to severe disease. It is imperative to continue to follow the long-term outcomes in these patients to assess the risk versus benefit of tocilizumab.

Corticosteroids

Similar to other severe respiratory tract infections, there is significant interest and controversy surrounding the role of corticosteroids for the management of severe pneumonia due to coronaviruses. The potential benefit of these agents to blunt the inflammatory cascade seen in severe disease needs to be carefully weighed against the concerns for secondary infections, adverse events, and other complications of corticosteroid therapy. The data assessing the role of corticosteroids as adjunctive care for severe coronavirus (SARS-CoV-1, MERS-CoV, and SARS-CoV-2) pneumonia are difficult to interpret. Given the retrospective observational nature of these analyses, there is significant confounding by indication that is difficult to control or correct for in addition to limited sample sizes. Patients who receive corticosteroids have a higher severity of illness, are more likely to require invasive interventions, and are more likely to be receiving intensive care. In addition, there is significant heterogeneity with regard to timing of corticosteroid initiation, which can significantly impact disease progression and likelihood of response. All of these features lead to patients who receive steroids being at increased risk for poor outcomes. In addition, there is great variation in agent and dosage used, which can impact both safety and efficacy. Therefore, clinicians making any therapeutic decisions based on the literature for corticosteroids need to keep these considerations in mind.

The clinical data for use of corticosteroids in SARS-CoV-1 infections are mixed. Multiple analyses show no impact on outcomes [47], one report demonstrates decreased mortality in critically ill patients [48], and others have documented worse outcomes for patients receiving steroids, including increased time to viral clearance [49] or an increase in the composite endpoint of ICU admission or death [50]. In MERS-CoV, receipt of corticosteroids has been associated with a delayed time until viral clearance in a large cohort (n = 309) of infected patients [51]. However, this same data set showed a nonsignificant reduction in 90-day mortality in patients receiving corticosteroids (adjusted odds ratio = 0.75; 95% CI, 0.52–1.07) after accounting for differences between the groups in a regression model accounting for time-varying exposures. Finally, recent evidence in SARS-CoV-2 suggested a decrease in mortality in patients with ARDS with the receipt of corticosteroids (23 of 50 [46%] vs 21 of 34 [62%] without; hazard ratio, 0.38; 95% CI, 0.20–0.72) [52].

As demonstrated, the data for corticosteroids are inconsistent, confusing, and inconclusive. Although target patients in whom corticosteroids will improve outcomes may exist (eg, those with cytokine-related lung injury who may develop rapidly progressive pneumonia), that population remains ill-defined [53]. Clinicians need to carefully weigh the risks and benefits of corticosteroids on the individual patient level. This need for a risk-benefit assessment in individual patients and careful consideration of dose is exemplified in the COVID-19 Diagnosis and Treatment Guide from the National Health Commission of the People's Republic of China where the authors state, "Based on respiratory distress and chest imaging, may consider glucocorticoid that is equivalent to methylprednisolone 1–2 mg/kg/day for 3–5 days or less. Note that large-dose glucocorticoid suppresses immune system and could delay clearance of SARS-CoV-2." [29] A recent consensus statement from the Chinese Thoracic Society recommends a lower dose, ≤0.5–1 mg/kg per day methylprednisolone for ≤7 days in select patients, after

careful consideration of risks and benefits [53]. Randomized controlled trial data are urgently needed to clearly define the role of corticosteroids in COVID-19.

PHARMACOLOGICAL TREATMENTS IN WHICH RISKS OUTWEIGH BENEFITS

Ribavirin With or Without Interferon

Ribavirin, a guanosine analog that terminates RNA synthesis, was first approved in the 1980s and has been used clinically for respiratory syncytial virus, viral hemorrhagic fever, and in combination with interferon for hepatitis C. As mentioned previously (see LPV/r section), it was evaluated against SARS-CoV-1 in 2003 and used clinically in combination with corticosteroids and/or interferon in the absence of other treatment options; however, outcomes were either poor or ill-defined [54, 55]. The doses required for antiviral activity against SARS range from 1.2 to 2.4 grams by mouth every 8 hours, which are associated with excessive toxicity to patients [56]. Wang et al [3] evaluated the in vitro activity of ribavirin against SARS-CoV-2 and found an EC_{50} of 109.5 μM, which was over 100 times less potent than remdesivir. The risk of hematologic toxicity at high doses likely outweighs potential clinical benefit, and therefore ribavirin was not considered a viable candidate for further investigation by the WHO research and development plan for SARS-CoV-2 given its lack of in vitro efficacy, toxicity profile, and poor outcomes.

Interferons (α, β) may stimulate innate antiviral responses and are expected to have in vitro activity against SARS-CoV-2, given the previously described activity demonstrated against MERS-CoV (EC_{50} 175 IU/mL). However, toxicities are substantial including severe cytopenias, hepatotoxicity (including fatality), neuropsychiatric events, and risk of developing fatal or life-threatening ischemia or infection, particularly when combined with ribavirin. This combination was not associated with improved mortality or enhanced viral clearance in a retrospective analysis of patients infected with MERS-CoV who were initiated on combination therapy within 1–3 days of ICU admission [57]. Despite the limited to poor data, Chinese guidelines recommend ribavirin 500 mg IV 2–3 times daily in combination with LPV/r or inhaled interferon-α (5 million units nebulized twice daily) as one of the "standard treatment" options for COVID-19. Various combinations of ribavirin, interferon, and other antiviral agents are currently being studied in several clinical trials.

Based on the poor in vitro activity, an absence of animal or human data supporting its use, and a significant toxicity profile, we recommend avoiding use of ribavirin in patients with COVID-19 at this time. Although interferons may be useful as adjunctive care, they pose a significant risk to critically ill patients, and in the absence of supportive data they also cannot be currently recommended.

Oseltamivir and Baloxavir

Given their antiviral activity against influenza, considerable attention has been paid to oseltamivir, and to a lesser degree baloxavir, as potential treatment options for COVID-19. This was exacerbated by the initial report from Huang et al [1] in Wuhan where patients managed with COVID-19 received oseltamivir in addition to broad-spectrum antimicrobials. It is important to note that use of oseltamivir was not as targeted therapy of SARS-CoV-2 but rather driven by the lack of a knowledge of the causative pathogen at the time of treatment and the desire to empirically treat influenza. The authors do not suggest the use of oseltamivir for COVID-19 in that publication, and there are no data that suggest in vitro activity of oseltamivir against SARS-CoV-2. In fact, the only data assessing oseltamivir activity against coronaviruses demonstrated it to be ineffective at inhibiting SARS-CoV-1, even at a concentration of 10 000 μM/L [56]. Coronaviruses do not utilize neuraminidase, and thus there is no enzyme to be inhibited by oseltamivir. This would hold true for zanamivir, peramivir, or any other neuraminidase inhibitor agents. Similarly, neither a defined mechanism nor in vitro data have suggested that baloxavir would demonstrate activity against SARS-CoV-2 or other coronaviruses. Therefore, given the critical need for these agents in the management of influenza and concern for drug shortages with oseltamivir, these agents should be avoided in patients with COVID-19 once influenza has been ruled out.

AGENTS UNDER INVESTIGATION FOR SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2

Table 2 lists agents that are being investigated and/or theoretically considered for the management of SARS-CoV-2-infected patients. At this time, no recommendation can be made for any of these agents. In general, they should be avoided without additional supporting evidence.

CONCLUSIONS

Appropriate management strategies for patients with COVID-19 are a rapidly evolving therapeutic challenge, and the optimal agents (if any) to treat infection or prevent progression to critical illness remain ill-defined. Although certain agents listed in this review are encouraging, and the potential benefit of therapy likely outweighs the relatively minor risk of adverse events from short-course therapy, the evidence remains inconclusive and changes almost daily.

Patient populations who warrant therapy and the timing of initiation of therapy need to be defined. Given that disease progression can occur rapidly in stable patients and that viral loads are highest early in the infection course, the authors of this review opine that rapid initiation of therapy in high-risk populations (patients who are hospitalized or outpatients who are at high risk

Table 2. Agents Under Investigation for SARS-COV-2

Agent	Comments
Anakinra	Interleukin-1 (IL-1) receptor antagonist hypothesized to quell cytokine storming. No data for use as adjunctive therapy for COVID-19 currently. No clinical trials are enrolling in China or the United States exploring this agent.
Arbidol (Umifenovir)	Antiviral used in Russia and China for influenza, being studied in Chinese clinical trials (200 mg by mouth 3 times daily for no more than 10 days) for COVID-19 claiming potent in vitro activity. No clinical data exist currently; not available in the United States.
Baricitinib	A Janus kinase family (JAK) enzyme inhibitor, suggested as a COVID-19 treatment from artificial intelligence [58]. No clinical data exist.
Bevacizumab	Recombinant humanized monoclonal antibody that prevents vascular endothelial growth factor (VEGF) association with endothelial receptors Flt-1 and KDR approved for multiple cancers in the United States. Is on critical, national shortage. Being evaluated in a clinical trial in China for COVID-19 (NCT04275414), no data exist at this time to support use.
Brilacidin	A host defense peptide mimetic in clinical development by Innovation Pharmaceuticals. The company recently announced they will begin testing the molecule against SARS-CoV-2 beginning the week of March 16, 2020.
Convalescent plasma	Convalescent plasma from patients who have recovered from viral infections has been used previously for SARS-CoV-1, Middle East respiratory syndrome, Ebola, and H1N1 influenza with reported success [59]. The safety and efficacy of convalescent plasma transfusion in SARS-CoV-2-infected patients has not been established, and no protocols exist currently in the United States. Protocols are reportedly being developed at The Johns Hopkins University Hospital.
Darunavir/cobicistat	HIV-1 protease inhibitor currently being evaluated in a clinical trial (NCT04252274), but no in vitro or human data exist to support use at this time.
Disulfiram	Thiuram derivative that blocks alcohol oxidation. Demonstrated ability to competitively inhibit the papain-like proteases of SARS; however, no clinical data exist [60]. No in vitro or clinical data exist for COVID-19.
Eculizumab	Humanized, monoclonal IgG antibody that binds to complement protein C5 and prevents formation of membrane attack complex (MAC). Being evaluated in a clinical trial (NCT04288713) for COVID-19 to quell immune response, no data exist at this time to support use.
Favipiravir	RNA-dependent RNA polymerase inhibitor with broad-spectrum antiviral activity; however, demonstrated high EC_{50} (decreased potency) against SARS-CoV-2 but was effective in protecting mice against Ebola virus despite similarly high EC_{50} values [3]. Currently being evaluated in Clinical Trial NCT04273763 for patients with COVID-19. This agent is not FDA approved or available in the United States.
Galidesivir (BCX4430)	Nucleoside RNA polymerase inhibitor with reported wide spectrum of antiviral activity, currently in pipeline of Biocryst Pharma and previously evaluated for Ebola and other hemorrhagic fever virus infections.
Griffithsin	Algae-derived lectin and potent HIV entry inhibitor agent that demonstrated in vitro activity against SARS-CoV-1 [61].
IVIG	IVIG remains on critical national shortage in the United States. The benefit in patients with COVID-19 is unclear.
Nelfinavir	Nelfinavir, an HIV-1 protease inhibitor, might be active against SARS-CoV-2 based on a preprint publication that utilized homology modeling [62]. No clinical data exist.
Niclosamide	Anthelminthic drug with in vitro efficacy against SARS-CoV-1; however, low absorption and oral bioavailability resulting in a wide range of serum concentrations in healthy volunteers after a single dose may limit utility as antiviral treatment [63].
REGN3048	Human monoclonal antibody discovered by Regeneron that reportedly binds to the S protein of MERS-CoV. Currently in phase 1 trial in healthy volunteers (NCT03301090). The company reportedly announced recruitment for phase 2 and 3 trials for SARS-CoV-2; however, these are not registered on ClinicalTrials.gov.
Sarilumab	IL-6 receptor antagonist FDA-approved for rheumatoid arthritis. Recently announced a US-based trial will begin enrolling at medical centers in New York for patients with severe COVID-19 disease.
Sofosbuvir	Antiviral used to treat hepatitis C, in vitro activity against SARS-CoV-1, no clinical data exist [64].
TZLS-501	A novel, fully human anti-IL6R by Tiziana Life Sciences. The company recently announced they are moving forward with clinical development for patient use in patients with COVID-19 and excessive IL-6 production.
Vitamin C	There is an ongoing clinical trial of 12 grams IV BID vitamin C in China for treatment of COVID-19 (NCT04264533). Use of this agent is not recommended at this time.
XueBiJing	Chinese herbal medicine extract infusion formulation given at 100 mL IV twice daily, suggested as a "may consider" treatment for severe and critical cases in the National Health Commission of the People's Republic of China: the COVID-19 Diagnosis and Treatment Guide, 7th Edition. This previously demonstrated improved mortality in patients with severe community acquired pneumonia in China [65].

Abbreviations: BID, twice a day; COVID-19, coronavirus disease 2019; EC_{50}, half-maximal effective concentration; FDA, US Food and Drug Administration; HIV, human immunodeficiency virus; IgG, immunoglobulin G; IL6R, IL-6 receptor; IV, intravenous; IVIG, intravenous immunoglobulin; MERS-CoV, Middle East respiratory syndrome coronavirus; RNA, ribonucleic acid; SARS-CoV, severe acute respiratory syndrome coronavirus.

of complications) is rational and should be considered, ideally in the context of a well-controlled, adequately powered trial. More important, however, this strategy is not without risk and needs to be weighed against potential adverse events (that remain poorly defined) and impending drug shortages with increases in use of these agents. To help address these concerns, careful consideration should be given to duration of therapy with many clinical trials and institutional protocols recommending 5–7 days for uncomplicated disease. Duration of therapy should be individualized to the patient and the progression of disease.

Clinicians must continually monitor and adapt as new literature becomes available. Caution should be applied because the bulk of the available clinical data are uncontrolled, not peer reviewed, or even unpublished. Given these

limitations, it is critical that institutions and clinicians report their experiences with the management and treatment of COVID-19 to the medical community so that we may further modify and optimize treatment recommendations and pathways.

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