COVID-19 Treatment: Updates March 19-24, 2020

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Clinicians and researchers across the globe are working with fervor to mitigate the world pandemic caused by SARS-CoV-2, the virus responsible for coronavirus disease 2019 (COVID-19). New data emerge daily, and it is imperative we embrace a deliberate calm to scrutinize the evidence and report it intentionally, despite our overwhelming desire to find an effective treatment. We previously reviewed published literature on experimental treatments for COVID-19 from December 31, 2019 through March 19, 2020. Here, we provide updates from the past 6 days (!!) as we strive to continually analyze data and optimize patient care. We also encourage readers to check out resources from the Society of Infectious Diseases Pharmacists (SIDP) regarding previously reviewed agents with therapeutic potential for COVID-19.

Changes to remdesivir access

On March 22, 2020, Gilead updated its website and stated the company is "transitioning the provision of emergency access to remdesivir from individual compassionate use requests to expanded access programs" due to exceedingly high demand for the drug. During the transition period, the company is processing compassionate use requests received prior to the announcement date and focusing on building an expanded access programs with regulatory bodies throughout the world. They are not accepting new compassionate use requests at this time, except for pregnant women or children less than 18 years old; however, enrollment in clinical trials is still an option in select locations.

Launching of national and global trials

The World Health Organization (WHO) announced the launch of a worldwide adaptive, randomized trial called SOLIDARITY. It consists of 5 treatment arms: remdesivir, chloroquine/hydroxychloroquine, lopinavir/ritonavir (LPV/r), LPV/r plus interferon-beta, or standard of care. Physicians treating patients with confirmed COVID-19 infection can enroll the individual into the trial by entering patient data into the WHO's website and providing a scanned copy of a signed patient consent form. Based on medications available at the enrolling hospital, the system will randomize the patient to a treatment arm or local standard of care. Current participating countries reportedly include Argentina, Bahrain, Canada, France, Iran, Norway, South Africa, Spain, Switzerland and Thailand.

In Europe, a similar adaptive trial, DISCOVERY, is also ongoing, coordinated by the French National Institute of Health and Medical Research (INSERM). The trial aims to enroll 3200 European patients from Belgium, France, Germany, Luxembourg, Netherlands, Spain, Sweden, and United Kingdom. The treatment arms are identical to the WHO trial except only hydroxychloroquine (HCQ) will be used (chloroquine is not an option). Australian researchers are also mobilizing randomized, controlled trials across 50 or more hospitals in their nation to evaluate potential COVID-19 treatments.

David Boulware, MD, MPH, at the University of Minnesota is coordinating an open enrollment trial of post-exposure prophylaxis with HCQ for health care workers or household contacts in the United States. Eligible participants email covid19@umn.edu directly for randomization to HCQ 800mg by mouth once, following in 6-8 hours by 600mg, then 600mg once daily for 4 consecutive days versus placebo. Recently, Todd Lee, MD, MPH, FIDSA, announced operationalizing a similar trial in Canada in just 8 days.

On March 24, 2020, The US Food and Drug Administration (FDA) stated they will accept single patient emergency Investigational New Drug Applications (eINDs) applications for use of convalescent plasma in patients with serious or immediately life-threatening COVID-19 infection. Convalescent plasma may contain antibodies to SARS-CoV-2 that might help fight disease, although it has never been proven beneficial for other viral illnesses. Potential donors must have complete resolution of symptoms at least 14 days prior to donation, documented negative SARS-CoV-2 from 1 or more nasopharyngeal or blood specimens, and SARS-CoV-2 neutralizing antibody titers, optimally greater than 1:320. Information for donation and use request are found here.

Finally, scientists in the Netherlands announced on March 23, 2020 they are recruiting 1000 health care workers from 8 Dutch hospitals to receive either bacillus Calmette-Guérin (BCG) vaccine or placebo to study if the vaccine is efficacious in preventing COVID-19 infection by augmenting the immune system.

Newly published literature

Cao B, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19.

Cao and colleagues conducted a randomized, controlled, open label study of hospitalized patients with confirmed COVID-19 comparing LPV/r (N = 99) 400/100 mg PO twice daily and standard care (N= 100). Standard care consisted of supplemental oxygen, ventilation, antibiotic therapy, vasopressor support, renal replacement therapy, and extracorporeal membrane oxygenation as necessary. Systemic glucocorticoids were administered in about a third of study patients and similarly between the treatment arms.

The primary outcome was time to clinical improvement, defined as the time from randomization to an improvement of 2 points on a 7-category ordinal scale or live discharge from the hospital, whichever came first. Secondary outcomes included 28-day mortality, length of stay, and time to virologic clearance. In order to assess viral clearance, serial oropharyngeal swab samples were obtained on day 1 and on days 5, 10, 14, 21, and 28 until discharge or death had occurred. The primary analysis was in the intent to treat population (N = 99 LPV/r, N = 100 standard care). Of note, 5 patients in the LPV/r arm did not receive therapy with LPV/r; 3 due to death prior to administration of study drug and 2 because the physician refused therapy after randomization. The 3 deaths were accounted for in a modified intent to treat analysis where these patients were excluded. However, the other 2 patients are included in all assessments despite not receiving therapy.

The median (IQR) age of the population was 58 (49 – 68) years and comorbidities were infrequent. Ninety-two percent of patients presented with a fever, 19% with a respiratory rate > 24 breaths/minute, and 1% with a systemic blood pressure < 90 mm Hg. The most common baseline score on the 7-category scale was 4 (hospitalization, requiring supplemental oxygen, 70%). The median (IQR) days from illness onset to randomization was 13 (11-16), and the mean baseline viral load was 4.0 ± 2.1 $\log_{10}$. There were no differences between the 2 groups in any of these baseline measures.

There was no difference in time to clinical improvement between LPV/r (median 16 (IQR 13-17) days) and standard care (16 (IQR 15-18) days; p= 0.09) in the intent to treat analysis. While the result became statistically significant in the modified intent to treat analysis (15 [13-17] days in the LPV/r group and 16 [15 – 18] days in the standard care arm), the impact would be of limited clinical importance. Although the authors state in the originally published text on March 19, 2020 “in the intention-to-treat population, LPV/r treatment within 12 days after the onset of symptoms was associated with shorter

time to clinical improvement (hazard ratio, 1.25; 95% CI, 1.77 to 2.05), but later treatment with LPV/r was not (hazard ratio, 1.30; 95% CI, 0.84 to 1.99)", a closer examination of the data (and the supplementary figure, S2) demonstrates a transcription error. The lower bound of the 95% confidence interval for "treatment within 12 days" should be 0.77, and thus, is not significant. This was corrected by the journal on March 25, 2020.

Twenty-eight-day mortality was numerically lower for LPV-r treated patients in the intent to treat (19.2% vs. 25.0%; difference – 5.8%, 95% CI – 17.3 to 5.7) and the modified intent to treat (16.7% vs. 25.0%; difference – 8.3%, 95% CI – 19.6 to 3.0) although these numbers failed to reach statistical significance and the study was not powered to assess mortality. Although ICU length of stay appears to be shorter with the addition of LPV/r (median 6 (IQR 2- 11) days versus 11 (IQR 7 – 17) days with standard care), closer examination suggests that this is driven by non-survivors treated with LPV/r dying sooner than control patients and when this analysis is limited to survivors the ICU length of stay is similar between LPV/r (9 (5-44) days) and standard care patients (11 (9-14) days). Additionally, there were no differences in viral eradication between the 2 arms on sampling day 5, 10, 14, 21, or 28. Rates of adverse events were also similar between the 2 groups.

In summary, this study failed to demonstrate any meaningful impact on outcomes in COVID-19 patients with the addition of LPV/r to standard care. Although the authors should be applauded for conducting a randomized controlled trial so rapidly, these data unfortunately do not greatly inform practice. First, the time from symptom onset until randomization was 13 days. If antiviral therapy were to influence disease course, it is more likely to be beneficial earlier, when viral replication is higher, rather than 2 weeks into illness. In SARS-CoV-1 infection, addition of LPV/r to the therapeutic regimen decreased mortality when used as initial therapy, but not when used as rescue/salvage therapy. Additionally, even though it failed to reach statistical significance, therapy with LPV/r was associated with a 33% absolute reduction in mortality when compared to standard care. One is left to wonder if an adequately powered study might have demonstrated significance. However, it is also hard to imagine why there would be a mortality advantage in the absence of quicker resolution or viral eradication, but alas without further description it is impossible to assess.

Gautret P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial.

The authors report on the first 42 patients of an ongoing, open-label study being performed at 4 different sites in France assessing the impact of HCQ 200 mg every 8 hours (600mg/day) versus standard of care in SARS-CoV-2 positive patients 12 years of age or older. Eligible patients were enrolled from Méditerranée Infection University Hospital Institute. Controls were either patients who refused treatment at that site or those managed at 1 of 3 other sites. Standard care consisted of symptomatic treatment and antibiotics to prevent bacterial superinfection at the discretion of the clinician.

The primary outcome in this initial report was virologic clearance in nasopharyngeal swabs at day 6 post-inclusion, with enrollment being day 0. Virologic clearance was defined as a cycle threshold > 35 by real-time reverse transcription-PCR. Secondary outcomes consisted of time to virologic clearance, clinical resolution, length of stay, mortality, and incidence of adverse events. However, only virologic results are presented in this manuscript.

Forty-two patients met the inclusion criteria in this study (N = 26 for HCQ, N = 16 control). Per the authors, 6 HCQ patients were "lost to follow up" because of early cessation of treatment. However, it warrants comment that this consisted of 3 patients that were transferred to the ICU while still PCR positive, 1 patient who died (PCR negative) on day 3, 1 who left the hospital (PCR negative) on day 2, and 1 patient who stopped treatment of day 3 due to nausea while still PCR positive. Since these patients could not be assessed for viral eradication on day 6, they were excluded from the analysis, leaving 20 HCQ treated patients in the study along with 16 untreated controls. HCQ treated patients were older (51.2 +/- 18.7 vs. 37.3 +/- 24.0; *P*=.06) and the time between onset of symptoms and inclusion was roughly 4 days in both groups.

HCQ treated patients experienced higher rates of viral eradication at day 6 post inclusion when compared to controls (14/20 (70%) vs. 2/16 (12.5%); *P*= .01). This difference was also evident at day 3 (50% vs. 6.3%; *P*=.005), day 4 (60% vs. 25%; *P*=.04), and day 5 (65% vs. 18.8%; *P*=.006). There was no separation between the groups on day 1 *(P*=.55) or day 2 (*P*=.23). The authors then divided the HCQ patients between those who received monotherapy (N = 14) and those whom received combination with azithromycin (N = 6). The authors demonstrated that clearance rates on day 3 (83.3% vs. 35.7%), day 4 (83.3% vs. 50%), day 5 (100% vs. 50%), and day 6 (100% vs 57.1%) were numerically higher in patients receiving combination therapy. The authors then go on to state that "for ethical reasons and because our first results are so significant and evident we decide to share our findings with the medical community, given the urgent need for an effective drug against SARS-CoV-2 in the current pandemic context" and "we therefore recommend that COVID-19 patients be treated with HCQ and azithromycin to cure their infection and to limit the transmission of the virus to other people in order to curb the spread of COVID-19 in the world."

Unfortunately, this bold proclamation is not supported by this data set. First, the authors failed to report any clinical outcomes. The relevance of viral eradication in nasopharyngeal swabs on a given day as it relates to clinical course or the spread of the virus is currently unknown. To illustrate this point, 1 of the patients on combination therapy who was swab negative on day 6 was positive on day 8. Second, whether the authors demonstrated viral eradication is at the very least debatable. Limited data suggest that the nasopharynx is not the most sensitive sample site for detecting SARS CoV-2 and the definition of negative used in this study, a cycle threshold (C_T) >35, is on the lower end of a range to define negativity, with others suggesting a C_T of 40 as the cutoff.

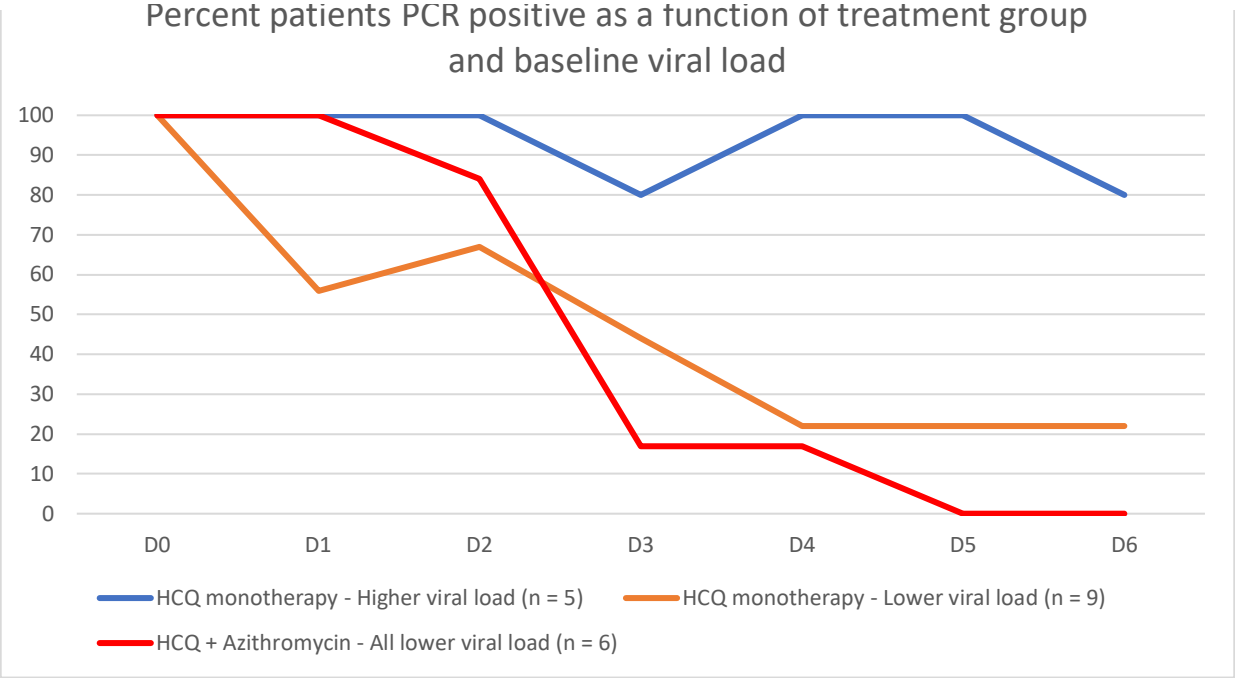
Third, as this study only focused on virologic clearance at day 6 post inclusion, the investigators made the decision to exclude patients who were not evaluable on day 6. This is problematic as patients who are transferred to the ICU, die, or discontinue therapy due to an adverse event, effectively fail therapy. At the very least a sensitivity analysis where these patients were considered failures is warranted. It is notable that this "drop-out" only occurred in HCQ treated patients and that the control arm did not suffer these early deaths or progression of illness excluding further swabbing. This suggests potential imbalance in study arms, treatment differences between institutions, or failure of HCQ. Unfortunately, this is impossible to interpret due to a rush to publication.

Fourth, there are some notable differences between the control arm and the treatment arm with regards to viral testing, presumably arising from the fact that most control patients were managed at different sites. While all patients in the HCQ arm have C_T values reported throughout the study duration to allow assessment, only 6 of the 16 control patients (4 of whom were asymptomatic) have such values. The other 10 patients (63%) simply have listed "positive" or "negative" making interpretation difficult as

viral loads cannot be assessed. Even more concerning, 10 control patients did not have nasopharyngeal swabs obtained on at least 50% of the observation days, including 1 who did not have a swab obtained on the day of enrollment or post inclusion days 1 or 2. How this patient was eligible for this analysis is unclear. Although largely uninterpretable, it is interesting that eradication at day 6 (primary endpoint) occurred in 2 out of 6 (33%) of control patients that had viral loads numerically determined and consistent measurements performed versus 0 out of 10 (0%) patients where this didn't occur; with this latter subgroup presumably being patients at a different institution.

Finally, and most importantly, the HCQ monotherapy and HCQ plus azithromycin group were not created equal. When examining baseline viral loads, it becomes apparent that a significant proportion of HCQ monotherapy patients had higher viral loads, as reflected by lower C_T values. All combination therapy patients have baseline C_T values ≥ 23, whereas in the monotherapy arm 5 patients (36%) have values < 23 (15, 17, 19, 22, 22) with the other 9 having comparable viral loads (CT values ≥ 23). Even in these small sample sizes, the impact of these differences, displayed in the figure below, is staggering. When removing the 5 patients on monotherapy with higher viral loads where almost no impact was seen on viral eradication, the eradication curves for monotherapy and combination therapy become nearly superimposable. There is not even a hint of superiority to combination therapy. When this finding is combined with an absolute lack of supporting evidence that would even suggest that azithromycin would play a role in COVID-19, it is inappropriate to suggest this combination should be applied to patient care at this point. Additionally, the potential additive cardiac toxicity and need to practice responsible antimicrobial stewardship during this critical time in health care further argue against combination therapy.

Given the limitations to the control group and the lack of clinical data provided, it is difficult to ascertain whether these data support HCQ as a therapeutic option for COVID-19. While we anxiously await the final, full results from this study, clinicians should be hesitant to currently utilize this information provided in order to support a therapeutic regimen.



Cai Q, et al. Experimental treatment with favipiravir for COVID-19: an open-label control study.

Favipiravir (T-705), an antiviral agent made in Japan with in vitro activity against several RNA viruses including SARS-CoV-2, was evaluated by Cai and colleagues in an open-label, nonrandomized control study of non-severe, non-ICU patients with COVID-19 in China. Consecutively screened patients admitted from January 30-February 14, 2020 received favipiravir 1600mg by mouth twice daily on day 1, followed by 600mg by mouth twice daily. This group was compared to "control" patients admitted from January 24-30, 2020 who received LPV/r 400mg/100mg by mouth twice daily; the reason for change in institutionally administered antiviral therapy on January 30 was not described. In both groups, patients received adjunctive inhaled interferon-α (5 million units BID) and standard care. Antiviral therapy was administered until confirmed viral clearance or until 14 days had passed, whichever was sooner. To be eligible for inclusion, patients had to be enrolled within 7 days of disease onset, but the exact timing of antiviral initiation in relation to symptom onset was not described. Other inclusion criteria included age 16-75 years, respiratory or blood samples positive for SARS-CoV-2, ability to take oral medications, absence of end stage liver or kidney disease, and willingness to take contraception through 7 days after treatment completion due to the teratogenicity of favipiravir.

Treatment efficacy was assessed by 1) time of viral clearance and 2) improvement of chest computed tomography (CT) on day 14 after treatment, using previously defined CT scoring criteria from patients with H1N1 influenza and SARS-CoV-1. Patients were deemed to improve if their 14-day CT score was lower than the value before medication initiation. Viral clearance was defined as 2 consecutive quantitative polymerase chain reaction (qPCR) negative results over a 24-hour interval; however, cycle threshold (Ct) for negativity and specimen type were not defined.

Overall, the authors enrolled 35 patients in the favipiravir arm, and 45 patients received LPV/r. Patients were excluded mostly due to age or duration of symptoms greater than 7 days. It was reported that all patients completed therapy and were followed for 14 days after treatment began, but average duration of antiviral medication was not reported. There were no statistically significant differences in baseline characteristics between groups. Median chest CT score at baseline was 12 vs 10 in the favipiravir and LPV/r arms, respectively.

Median time to viral clearance for patients receiving favipiravir was 4 days (IQR 2.5-9) which was significantly earlier than LPV/r-treated patients (11 days (IQR 8-13); $P < 0.001$). On day 14 after treatment, 91.4% of patients treated with favipiravir demonstrated improvement in chest CT compared to 62.2% of patients treated with LPV/r. Patients with viral clearance within 7 days of treatment had significantly higher improvement rates than patients with delayed clearance. A multivariate analysis found T lymphocyte count and antiviral treatment with favipiravir versus LPV/r (HR 3.434, 1.162-10.148) were independent factors that affected viral clearance. Favipiravir treatment was also associated with greater improvement in chest CT in a separate multivariate analysis (OR 3.190, 1.041-9.78). Finally, more adverse events occurred in the LPV/r group (25) compared to favipiravir (4); the most comment events were gastrointestinal in nature (nausea, vomiting, diarrhea).

While these data are encouraging for the potential of favipiravir and another "red flag" for LPV/r, these data are limited by the non-randomized, non-controlled, single center nature and inevitable selection bias in patient recruitment. Additionally, the lack of clarity on time to drug initiation, specimen used to determine viral clearance, and degree of initial viral load in relation to treatment response make these results difficult to interpret. The CT changes in patients were classified as only "improve", "worse", or "constant" but the degree of improvement was not delineated. Only 1 point was required to be

considered improved on the investigators scale, potentially overstating the impact of favipiravir on improvement. Median duration of treatment exposure was not defined in this cohort, which is important to clarify as the optimal duration of antiviral therapy remains unknown for SARS-CoV-2. It is possible that LPV/r-treated patients experienced more adverse drug events from longer drug exposure, since viral clearance was delayed and treatment was continued until viral eradication or 14 days, whichever was shorter.

Importantly, all favipiravir-treated patients were admitted at least a week after LPV/r patients. While this would not typically be significant, during a world pandemic a week of patient experience could significantly change clinicians understanding of the disease and systems or protocols for supportive care management, which may impact clinical course. Additionally, as patients and clinician's awareness of the disease increases over time, they may seek care and/or initiate therapy sooner. The authors do not report time from symptom onset to therapy initiation, so it is difficult to appreciate the impact this might have had on patient outcomes. Regardless, the importance of early viral clearance in disease resolution suggested in this study is intriguing and should be explored further. At this time, despite the noted limitations, these data suggest favipiravir may improve viral eradication and CT findings in patients with COVID-19 and further investigation of this agent is warranted. Favipiravir is only available in Asia, and the world will watch as randomized, controlled data emerge with use of this agent for treatment of COVID-19.

Liu J, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro.

In a letter to the editor, Liu and colleagues evaluated the antiviral potential of HCQ in vitro as a follow-up to their previous publication (first available online February 4, 2020) describing the in vitro activity of remdesivir and chloroquine against SARS-CoV-2. Hydroxychloroquine is an intriguing therapeutic option due to its lower propensity to cause cardiac toxicity and more readily available supply (for now). The authors demonstrated a 50% cytotoxic concentration (CC_{50}) of HCQ (249.50 µM) similar to chloroquine (273.20 µM), but less potent antiviral activity. The 50% maximal effective concentration (EC_{50}) at 4 different multiplicities of infection in VeroE6 cells at 48 hours were consistently higher for HCQ (4.51, 4.06, 17.31, 12.96 µM) compared to chloroquine (2.71, 3.81, 7.14, 7.36 µM), resulting in a lower selectivity index (CC_{50}/EC_{50}) for HCQ. Interestingly, the EC_{50} values demonstrated for chloroquine were higher than previously reported which the authors attributed to "adaptation of the virus in cell culture that significantly increased viral infectivity upon continuous passaging". These findings are also contrary to previous data suggesting HCQ is more potent than chloroquine against SARS-CoV-2. The authors sought to further characterize the mechanism of action of chloroquine and HCQ in inhibiting SARS-CoV-2 and found both drugs block transport of the virus from endosomes to endolysosomes, an essential step in viral shedding, but impact changes in number and size of these organelles differently.

No data exist to assess the relationship between an EC_{50} value, exposures of HCQ achieved in patients, and clinical outcomes. However, the authors note that reported concentrations achieved in human tissue, including lung tissue, at "safe dosage" (described as 6-6.5 mg/kg) far exceed laboratory-derived inhibitory concentrations and therefore in vivo antiviral activity may exist. The effective dose of HCQ, if one exists, remains unknown as does the ideal treatment duration and time of therapy initiation throughout the clinical course of COVID-19. The authors implore for carefully designed clinical trials to answer these questions.

Chen J, et al. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19).

An abstract of 30 "common" patients with COVID-19 was recently made available online in English, with the full text only available in Chinese. The following analysis is provided with the help of Siu Yan Amy Yeung, PharmD, BCPS, BCCCP, a pharmacist at the University of Maryland Medical Center who translated the main details of the study. The authors randomized patients 1:1 to receive HCQ (400mg PO daily x 5 days) plus conventional therapies or conventional treatment only (control group) with 15 patients assigned to each arm. Patients were screened, randomized, and started treatment on the day of admission. Notably, conventional treatment in China at the time of this study includes inhaled interferon-α, LPV/r, and/or umifenovir so almost every patient in both arms was on some other investigational antiviral therapy.

The primary end point was viral clearance based on samples from nasopharyngeal, sputum, or lower respiratory secretions or mortality within 2 weeks. Secondary endpoints included adverse drug event within 2 weeks and progression to severe or critical disease. The median duration from hospitalization and therapy initiation to SARS-CoV-2 nucleic acid negativity in respiratory pharyngeal swab was 4 days (range 1-9) for the HCQ-treated group compared to 2 days (range 1-4) in the control group; patients in both groups were afebrile after median 1 day of hospitalization. One patient in the HCQ group progressed to severe disease and 5 (33%) patients in the HCQ group had radiograph progression on CT compared to 7 (47%) patients in the control group. No deaths were reported in either group. Adverse events were similar between groups. The authors concluded that patients with "common" or mild COVID-19 had a good prognosis, and that further studies are needed with validated endpoints and larger sample size to determine if any benefit exists with HCQ treatment.

While these data suggest no benefit to the addition of HCQ to standard therapy (including other antivirals) for viral clearance, no real interpretation can be made. It is impossible to find a treatment effect in such a small, confounded data set and viral clearance is not a validated study endpoint for COVID-19 disease. Similar to our aforementioned caution in using the Gautret study to support HCQ, we would recommend exercising equal caution in using these data to refute it. The tolerability of HCQ in this small cohort is encouraging.

Cao W, et al. High-dose intravenous immunoglobulin (IVIG) as a therapeutic option for deteriorating patients with coronavirus disease 2019.

Cao and colleagues describe 3 patients with severe COVID-19 treated with high-dose IVIG (25 grams/day for 5 days). One patient started therapy on hospital day 7 (symptomatic day 9), the second patient on hospital day 2 (symptomatic day 11), and the final patient on hospital day 5 (symptomatic day 11). All experienced resolution of fever within 1-2 days and oropharyngeal swab viral nucleic acid negativity within 4-5 days of IVIG initiation. Patient 2 also received LPV/r, patient 3 received concomitant methylprednisolone. It is unclear the role of IVIG in the clinical course of these patients and use of IVIG for treatment of COVID-19 remains controversial, particularly when current IVIG formulations would not be expected to contain antibodies for SARS-CoV-2.

Alhazzani W, et al. Surviving sepsis campaign: Guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19).

The European Society of Intensive Care Medicine and the Society of Critical Care Medicine issued 54 statements on the management of critically ill adults with COVID-19 including topics such as infection

prevention, laboratory diagnostics, hemodynamic support, ventilatory support, and pharmacological therapies. Notably, the panel suggests using systemic corticosteroids over not using corticosteroids in mechanically ventilated adults with COVID-19 and acute respiratory distress syndrome (ARDS) (weak recommendation, low quality evidence) but suggests against corticosteroid use in patients with COVID-19 and respiratory failure without ARDS (weak recommendation, low quality evidence). They also suggest against the use of IVIG, convalescent plasma, and LPV/r. For all other antiviral and immunomodulatory medications, they state "there is insufficient evidence to issue a recommendation" on use in critically ill adults with COVID-19.

Conclusions

More than 450,000 cases of COVID-19 have been diagnosed across the globe with over 20,000 deaths. Although data are beginning to emerge regarding potential therapeutic options, the quality of the evidence remains weak and firm conclusions cannot be made. It is imperative to note that proven safe and effective therapy is currently limited to supportive care. As the emerging observational data is of limited utility in assessing the efficacy of different therapies for COVID-19, preference should be given to enrolling patients in randomized, controlled trials. In settings where clinical trials are not a realistic option, pharmacists, physicians, researchers, laboratory specialists, and other members of the health care team are obligated to assess emerging data and make informed, safe, team-based decisions to allow patients the best opportunity for a positive outcome.

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