Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Treatment Options for Coronavirus Disease 2019 in Patients With Reduced or Absent Kidney Function

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Coronavirus disease 2019, the disease caused by the severe acute respiratory syndrome coronavirus 2 virus, was first identified in the Hubei Province of China in late 2019. Currently, the only role for therapy is treatment of the disease, as opposed to post-exposure prophylaxis, however multiple clinical trials are currently ongoing for both treatment and prophylaxis. Treating coronavirus disease 2019 relies on two components; the first is inhibition of the viral entrance and replication within the body and the second is inhibition of an exacerbated immune response which can be seen in patients with severe disease. Many drugs have shown in vitro antiviral activity; however, clinical trials have not been as promising. This review summarizes the current data for the most commonly used drugs for coronavirus disease 2019 and will cover the unique factors that may affect the dosing of these medications in patients with CKD. While clinical trials are ongoing, most are in patients with normal kidney function. During a pandemic, when patients with CKD are at higher risk of both infection and death, it is imperative to include patients these patients in the clinical trials.

Key Words: COVID-19, SARS-CoV-2, Coronavirus, Treatment, Kidney dysfunction

In late 2019, a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified as the cause of a familial cluster of pneumonia in the Hubei Province of China.[1] Human-to-human transmission was identified, and it spread worldwide with cases in the United States first identified in January 2020.[2] On March 11, 2020, the World Health Organization declared coronavirus disease 2019 (COVID-19), the disease caused by SARS-CoV-2, a worldwide pandemic.[3] As of August 1, 2020, the virus has killed more than 675,060 people worldwide with more than 20% of those recorded deaths within the United States.[4]

SARS-CoV-2 is a positive-strand RNA virus belonging to the *Betacoronavirus* that also contains severe acute respiratory syndrome coronavirus (SARS-CoV) (virus cause of SARS) and Middle East respiratory syndrome coronavirus (MERS-CoV).[5] The virus uses its structural spike (S) protein to attack the target cells and binds to the host angiotensin-converting enzyme 2 protein. It is primed by the host transmembrane protease, serine 2 encoded by TMPRSS2 gene, to enter the cell using the host cell endosomes.[6] Viral polyproteins are then synthesized and encode for the replicase-transcriptase complex. RNA is synthesized via its RNA-dependent RNA polymerases. Proteins are then synthesized together leading to completion of assembly and release of viral particles.[7] An understanding of the viral mechanism of infection helps to identify potential drug targets as illustrated in Figure 1.

ROLE OF THERAPY

Multiple randomized controlled trials are ongoing to determine the efficacy of several therapies targeting SARS-CoV-2. Currently, there are limited data to determine which patients require therapy and which patients improve without complications. Known risk factors for severe disease include CKD, chronic obstructive pulmonary disease, cancer, immunocompromised state from solid organ transplant, serious cardiac disease, type 2 diabetes mellitus, and obesity (body mass index >30).[8-10] Progressive hypoxia and high inflammatory markers including C-reactive protein and ferritin are also associated with progression of disease.[11] Despite recognizing these risk factors, it is unclear if treatment early in disease is associated with improved outcomes. While current practice seems to be targeting patients at highest risk of progression, limited data are also available to identify the ideal candidate for therapy. Table 1 summarizes suggested drug dosing adjustment based on reduced kidney function. The Infectious Disease Society of America (IDSA) guidelines have rapidly changed as new evidence has emerged but currently recommend only the use of remdesivir and corticosteroids outside of clinical trial.[12]

Multiple studies are actively being performed to assess the need for post-exposure prophylaxis including use of remdesivir, and convalescent plasma. Although early in the pandemic, there was some excitement for the use of hydroxychloroquine prophylaxis, a recent randomized, double-blind, placebo-controlled trial evaluating hydroxychloroquine as post exposure prophylaxis did show no difference between hydroxychloroquine therapy vs placebo, and therefore hydroxychloroquine, is unlikely to provide postexposure protection.[13] While other trials are currently pending, the IDSA currently recommends against the use of prophylaxis therapy outside of the clinical trial setting.[12]

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Antiviral Considerations

Chloroquine/Hydroxychloroquine. Chloroquine is a widely used drug, commonly used for malaria therapy and autoimmune diseases including rheumatoid arthritis and systemic lupus erythematosus. Hydroxychloroquine is an analog of chloroquine with less drug interactions and less side effects. In SARS-CoV-2, chloroquine was hypothesized to block viral infection by increasing the endosomal pH required for virus/cell fusion leading to defective protein degradation, endocytosis, and exocytosis.[14,15] Studies performed in vitro showed that chloroquine and hydroxychloroquine both decreased the viral replication in a dose-dependent manner when given at treatment dosing; however, the inhibition rate was much lower when pretreated with hydroxychloroquine and chloroquine suggesting less of an effect if given as prophylaxis before infection.[16] Besides its antiviral properties, it also has some immunomodulation which could also be beneficial in treatment of COVID-19.

Based on the above observations, chloroquine and hydroxychloroquine were used as early therapies in the treatment of COVID-19, and its use was further propagated by a small, retrospective, biased study from France with 36 patients, which showed decrease in viral burden and improved outcomes in patients treated with hydroxychloroquine.[17] This small biased study received significant media coverage leading to high levels of nonevidence-based usage of hydroxychloroquine.[18] Since then, larger population studies have been released with the majority showing no benefit in the use of chloroquine and hydroxychloroquine. Examples include a study from Borba and colleagues[19] comparing high-dose vs low-dose chloroquine that was discontinued early owing to toxicity in the higher dosage group with no benefit identified. A retrospective study from the Veterans Affairs looked at hospitalized patients who received hydroxychloroquine and showed no evidence that use of hydroxychloroquine reduced the risk of progression of disease including mechanical ventilation and death.[20] This study also showed a higher risk of death associated with the hydroxychloroquine group; even after a calculated propensity score, there is a bias as the hydroxychloroquine group represented the sickest patients.[20] Multiple large observational studies of New York also found no differences in outcomes between patients treated with hydroxychloroquine and those with no therapy.[21,22] In May 2020, the Lancet published an article which showed patients treated with hydroxychloroquine had higher mortality and no benefit for therapy. This study, however, was later retracted by authors given concern of the validity of the database.[23] Other studies including a New England Journal of Medicine article on the relationship between mortality and angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers was also retracted for using the same database.

While the majority of the data associated with hydroxychloroquine has shown no difference, there was an article from Arshad and colleagues[24] that suggested a mortality benefit associated with the use of hydroxychloroquine and azithromycin. This was a retrospective study performed within 1 hospital system, but they found treatment with hydroxychloroquine alone improved mortality. More prospective clinical trials worldwide are ongoing; however, hydroxychloroquine is currently not recommended as therapy given the overwhelming negative data outside of this trial.

While azithromycin has no antiviral effects, the Gautret[17] study also described 6 patients who received dual treatment with azithromycin and hydroxychloroquine with 100% of these patients having negative nasopharyngeal test for presence of virus by day 6 using polymerase chain reaction (PCR) technique. Multiple further studies have not shown any difference in virologic clearance or clinical outcomes when treated with both hydroxychloroquine and azithromycin.[25] Furthermore, studies looking at QTc prolongation associated with combination of hydroxychloroquine and azithromycin showed a prolonged QTc in at least 30% of patients, with 11% of patients having a QTc longer >500 ms.[26] Based on these data, the current IDSA guidelines recommend against the usage of hydroxychloroquine with and without azithromycin outside of a clinical trial.

While hydroxychloroquine is nondialyzable and kidney clearance accounts for 15-25% of total clearance of hydroxychloroquine; no dose adjustment is recommended in patients with CKD or those on dialysis.[27]

CLINICAL SUMMARY

- While active trials are ongoing, there is currently no known benefit of providing postexposure prophylaxis.
- Active research is ongoing to determine the ideal treatment for coronavirus disease 2019, including antiviral therapy and immunomodulation.
- Patients with reduced kidney function are in a high-risk category and may need special attention for drug dosing/interactions.

REMDESIVIR

Recently, there has been significant interest in the usage of remdesivir; in vitro activity has been noted against other RNA viruses including the Ebola virus, Marburg, MERS-CoV, and SARS-CoV.[28] Remdesivir is an adenosine analog that inhibits RNA-dependent RNA polymerase by incorporating into the viral RNA chains causing premature termination.[29,30] In vitro data show that it can inhibit SARS-CoV-2 infection effectively in human cell lines.[30] In a nonhuman primate model, remdesivir prevented progression of disease both prophylactically and therapeutically.[31]

While multiple clinical trials are ongoing, some data have been released for remdesivir therapy. Compassionate usage

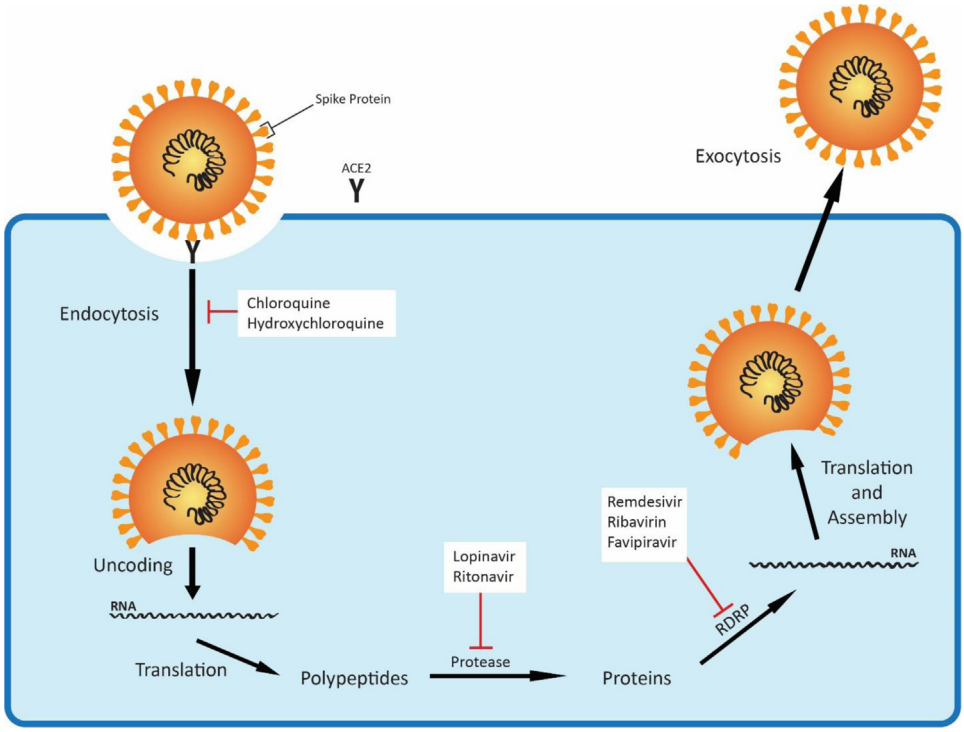

Figure 1. Mechanism of action of the drugs with possible antiviral activities. RDRP is RNA-dependent RNA polymerase. Abbreviation: ACE, angiotensin-converting enzyme.

data showed that patients with severe disease had a 68% improvement in oxygen-support class; however, this was just an observational study.[32] The Adaptive Covid-19 Treatment Trial (ACTT-1) was published in May 2020, which was a double-blind, randomized, placebo-controlled trial where they used intravenous remdesivir in hospitalized patients with COVID-19. With an enrollment of 1063, this was the largest clinical trial to date for remdesivir.[33] This study showed a 31% faster recovery (11 days for patients treated with remdesivir compared with 15 days for patients who received placebo). There was also a trend to survival benefit (mortality rate of 7.1% for remdesivir and 11.9% with placebo), however not significantly different.[33,34] Based on these data, the IDSA guidelines

Table 1. Potential Therapies for SARS-CoV-2 and Dosage Adjustment for Reduced Kidney Function

Drug Name	Mechanism of Action	Precautions	Kidney Implications
Hydroxychloroquine/ Chloroquine	Increases endosomal pH leading to defective protein degradation, endocytosis, and exocytosis	QTc prolongation. Caution in G-6-PD* deficiency	No kidney dose adjustment required
Remdesivir	Inhibits RNA-dependent RNA polymerase	Hepatic toxicity	Caution in patients with CrCl† < 30 mL/min, not studied SBECD carrier can accumulate.
Lopinavir/Ritonavir	Inhibits the cleavage of viral proteins	Drug-Drug interactions	No kidney dose adjustment required
Ribavirin			Contraindicated with CrCl <50 mL/min
Dexamethasone	Anti-inflammatory		No kidney adjustment
Tocilizumab/Sarilumab	Anti-IL-6	Avoid in patients with active tuberculosis	No kidney dose adjustment recommended CrCl < 30 mL/min not studied
JAK Inhibitors	Anti-JAK inhibitors	Increase risk of HSV and fungal infections.	Variable based on the inhibitor.

Abbreviations: IL, interleukin; JAK, Janus kinase; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
*G-6-PD: glucose-6-phosphate dehydrogenase deficiency.
†CrCl: creatinine clearance.

currently recommend antiviral therapy over nonantiviral therapy. Multiple other clinical trials are in process.

The pharmacokinetics of remdesivir in patients with kidney impairment has not been well studied. Clinical trials have included patients with a creatinine clearance greater than or equal to 30 mL/min and therefore no changes in dosing required.[35] Currently, there are no dosing recommendations for individuals on dialysis and with those with a creatinine clearance of less than 30 mL/min. The biggest concern in the patients with impaired kidney function is the accumulation of the SBECD (sulfobutylether-β-cyclodextrin) carrier.[36] SBECD is a large cyclic oligosaccharide whose accumulation in animal studies has shown to lead to liver necrosis and kidney tubular obstruction. SBECD is readily removed by hemodialysis and continuous renal replacement therapy. It is also speculated that a short course (eg, 5-10 days) is unlikely to cause such significant disease. Nevertheless, more data are needed in patients with kidney dysfunction.[36]

OTHER NUCLEOTIDE ANALOGS

Other drugs that affect the RNA polymerase include favipiravir, ribavirin, and EIDD-2801. Favipiravir is a pyrazine carboxamide derivative that inhibits the influenza viral RNA-dependent RNA polymerase. It currently holds approval for the treatment of influenza in both Japan and France.[37] In vitro studies have shown that favipiravir can inhibit viral proliferation.[30] An open-label study from China compared favipiravir with combination of lopinavir/ritonavir. Both groups received aerosolized interferon (IFN)–*a*. This study showed improved chest imaging and viral clearance in the favipiravir group.[38] Multiple clinical trials worldwide are currently ongoing for favipiravir.

Ribavirin is a guanosine analog. Studies on SARS-CoV showed some improvement of outcomes compared with historical outcomes when treated with ribavirin and lopinavir/ritonavir.[39] Another systemic review of 26 studies was inconclusive for the benefit of ribavirin for SARS-CoV.[40] High concentrations of ribavirin however were needed for viral suppression.[30] Further studies are needed. Use is contraindicated in patients with creatinine clearance of <50 mL/min.

EIDD-2801 is an experimental nucleotide analog drug that inhibits SARS-CoV-2 replication in a cellular assay.[41,42] It has been showed to be 2-10 times more potent than remdesivir in blocking SARS-CoV-2 replications in vitro.[29] Currently, no clinical data are available on this drug, and it is currently in early clinical trials.

PROTEASE INHIBITORS – LOPINAVIR/RITONAVIR

Lopinavir/ritonavir was originally developed for treatment of human immunodeficiency virus (HIV). It works by binding to protease and inhibiting the cleavage of viral proteins. Although SARS-CoV-2 has a different protease than HIV, studies have shown lopinavir/ritonavir has some in vitro activity against SARS-CoV-2.[43]

While still in clinical studies, currently, there is no clear clinical benefit of lopinavir/ritonavir. Early case studies showed that the usage of lopinavir/ritonavir caused reduction in coronavirus viral load.[44] In a small randomized, controlled, open-labeled trial of China, 199 patients were randomized 1:1 into standard therapy vs standard therapy with lopinavir/ritonavir. No differences were found in the clinical deterioration, time to clinical improvement, or duration of viral detectability. There was a numerically lower mortality rate, but the study was not powered to determine a significant difference in mortality.[45] Based on these studies, the IDSA guidelines recommend against the use of lopinavir/ritonavir outside of clinical trials.[12] Currently, as per the manufacturer's guidance, no dosage adjustment is needed for patients with CKD including those on kidney replacement therapy.

Because of the in vitro data, other protease inhibitors, including darunavir, were trialed, given a drug shortage of lopinavir/ritonavir. While unpublished, data released from Janssen, darunavir-cobicistat parent company, showed that darunavir has no in vitro activity against SARS-CoV-2.[46] Therefore, darunavir-cobicistat is not recommended as therapy for COVID-19.

MISCELLANEOUS

Many other drugs are currently under investigation for use in the treatment of COVID-19. Oseltamivir is a neuraminidase inhibitor used for influenza; however, neuraminidase is not found in the coronavirus, and although used in China and in some clinical trials, it is currently not recommended for usage.[8]

Nitazoxanide is a commercial antiprotozoal agent with a broad range of antiviral activity including coronavirus. In vitro, it also has some activity against SARS-CoV-2.[30] No in vivo data have been published to this point.

Ivermectin is a broad-spectrum antiparasitic agent that has also been shown to have some broad antiviral activity including activity against HIV-1, dengue virus, West Nile Virus, and influenza. In vitro studies have shown that ivermectin has some activity against SARS-CoV-2. No in vivo studies have been performed, and no clinical data are currently available.[47]

Immunological Considerations

While antiviral discovery and treatment is important, many of the pathological findings including acute respiratory distress syndrome are believed to be secondary to an extreme immune response. Early studies that compared patients with mild disease and patients with severe disease found that patients with severe disease had a higher ferritin, C-reactive protein, and interleukin (IL)-6, which lead to further treatment with these immunomodulators.[48,49] Symptoms described originally were suggestive of cytokine release syndrome that had been previously described in chimeric antigen receptor T cell (CAR-T cell) therapy.

Cytokine release syndrome has been well described in CAR-T cell therapy. It is associated with fever, organ dysfunction including acute kidney injury and hepatitis,

hypotension, and acute respiratory distress syndrome.[50] Given the similarities between COVID-19 and cytokine release syndrome, immune-modulating agents have been attempted as discussed in the following.

IL-6 BLOCKADE

Tocilizumab is a recombinant humanized monoclonal antibody that is directed against IL-6 receptor (IL-6R). Importantly, it binds both the IL-6R that is soluble and membrane bound. It was originally approved by the Food and Drug Administration for cytokine release syndrome associated with CAR T-cell therapy in 2019 based on some retrospective data.[51] In the CAR-T cell therapy, they showed significant improvement in the hypotension, oxygenation, and organ dysfunction.[51] Because of the correlation between cytokine release syndrome and COVID-19, tocilizumab was used early in the pandemic. An early observational study of 21 patients after treatment of tocilizumab showed improvement of fever, respiratory infection, and oxygen requirements; however, there was no control arm to this study.[52] A more recent retrospective case-control study of France showed a significantly lower mortality in patients treated with tocilizumab than those treated with standard of care.[53] Multiple clinical trials are currently ongoing.

Sarilumab is another IL-6 RA, which also binds the soluble and membrane-bound receptors. It is clinically improved for rheumatoid arthritis. Although no clinical data are present for sarilumab, multiple clinical trials are ongoing.

Both of these drugs are not metabolized through the kidney, and therefore, no changes in dosing is required for patients with kidney dysfunction, although limited data on patients with creatinine clearance of less than 30 mL/min are available.[54] IL-6 is an important cytokine in immunity against mycobacterium infections as well as hepatitis B infection, and therefore, testing for these infections is important before initiation of therapy if possible, and active disease is a contraindication to therapy. Other contraindications include greater than 1.5 times the upper limit of normal of the aspartate transaminase and alanine aminotransferase. Currently, the IDSA recommends use of tocilizumab only in the setting of a clinical trial.

JANUS KINASE INHIBITORS

The Janus kinase (JAK) inhibitors, ruxolitinib, tofacitinib, and baricitinib, are Food and Drug Administration approved for steroid-refractory graft vs host disease and rheumatoid arthritis.[55] Cytokine release syndrome is also treated with JAK inhibitors, spawning interest in their use for COVID-19 inflammatory response. These agents act through JAK1 and JAK 2 inhibition leading to inhibition of the IL-6 and IFN-g but also inhibit IL-2 and the IFN-a/b signaling cascade.[56] Clinical trials are currently ongoing looking at therapy with JAK inhibitors. Infection is a high concern for JAK inhibitors including increase risk of disseminated herpes simplex virus and fungal infections.[57,58]

INTERFERON

Interferon has been used in a variety of treatment models including hepatitis C and MERS-CoV. In a nonhuman primate model infected with MERS-CoV, treatment with IFN-*B*1b showed improved clinical scores and lower mean viral load.[59] IFN-*B*1b was used some in China at the initiation of the COVID-19. A more recent small open-labeled randomized trial of Hong Kong compared IFN-*B*1b was combined with lopinavir-ritonavir and ribavirin and lopinavir-ritonavir alone. Study found that the triple antiviral therapy shortened the duration of viral shedding and shortened the hospitalization in patients with mild to moderate disease. Further studies are needed at this time to determine if any true benefit in severe disease.[60]

CORTICOSTEROIDS – DEXAMETHASONE

Corticosteroids usage in COVID-19 was originally controversial because some data in SARS patients found no difference between steroid usage and no steroid usage in clinical outcomes, although studies were small and mostly nonrandomized.[40] One was a randomized, double-blind, placebo-controlled trial for patients with SARS that found delayed viral clearance if steroids were given at the first week of illness but found no clinical benefit of the steroids.[61] Another was a case-control trial that showed a higher risk of psychosis in patients treated with steroids and again no benefit noted.[62] Other studies have shown steroid use for SARS resulting in steroid induced diabetes mellitus and avascular necrosis. It was for these reasons corticosteroids were originally thought to be contraindicated in COVID-19 pneumonia.

More recently, benefit has been suggested from steroid usage in patients with acute respiratory distress in COVID-19 pneumonia. In the recovery trial, the use of dexamethasone at 6 mg/day for 10 days had a significantly improved mortality for those requiring mechanical ventilation at the time of randomization (29.3% vs 41.4% mortality) and those requiring oxygen (23.3% vs 26.2%).[63] This supported early observational studies that showed patients outside of acute respiratory distress had no improvement on steroids. Some studies even showed improved outcomes in progressive disease treated with methylprednisolone but for patients with acute respiratory distress.[64] Clinical trials are still ongoing to evaluate use of steroids during acute respiratory distress syndrome in COVID-19 pneumonia. The IDSA now recommends use of steroids in patients requiring oxygen.

CONVALESCENT PLASMA

Prior use of convalescent plasma has been trialed for other viruses including Ebola virus, MERS-CoV, SARS-CoV, H5N1 avian influenza, and H1N1 influenza.[65] Trials during the pandemic influenza A (H1N1) in 2009 showed treatment with convalescent plasma resulted in reduction of respiratory tract viral load, serum cytokine response, and mortality.[66] Of note, this was a cohort study and not a randomized control trial with control being patients who declined to get plasma. In COVID-19, a small case series of 5 patients who received convalescent plasma had

improvement of disease including improved respiratory requirements and decreased in respiratory viral loads, and 3 of 5 patients were discharged by day 37 after transfusion.[65] Another case control study with 10 controls had a 30% mortality group in the control group as opposed to no deaths in the convalescent plasma therapy group.[67] These case series were the basis of evaluation of convalescent plasma. Currently, there are multiple clinical trial ongoing using convalescent plasma for both treatment as well as prophylaxis therapy. These trials may also provide more data on its use in high-risk patient groups especially with CKD or kidney transplant recipients which may include remote risk of transmission of blood-borne diseases such as hepatitis B, hepatitis C, or HIV and of sensitization in a pretransplant recipient.[68]

VACCINE DEVELOPMENT

Currently, there are no vaccines available for the SARS-CoV-2 virus; however, multiple vaccines are actively in clinical trials. These include vaccines using an adenovirus vector encoding the spike protein for SARS-CoV2 (ChAdOx1 nCoV-19), which currently has shown promise. Studies using rhesus macaques showed that after a SARS-CoV-2 challenge, macaques that were prevaccinated had lower viral burden and developed no signs of clinical pneumonia.[69] This vaccine is currently in phase 3 trials in the United States.

Another vaccine currently showing promise is the mRNA-1273. In phase 1 clinical trials, this vaccine induced anti-SARS-CoV-2 immune responses in all participants.[70] Nonhuman primate studies have been performed using this vaccine as well, and they developed a robust SARS-CoV-2–neutralizing antibodies. These nonhuman primates also had significantly less pulmonary inflammation and reduced bronchoalveolar lavage viral loads.[71] This vaccine and other variations of this vaccine are in clinical trials throughout the United States.

SUMMARY

Since the first cases of COVID-19, a variety of treatment options have been tested. Currently, standard of care is supportive care; however, multiple clinical trials are ongoing, and therefore, recommended treatment of these patients is changing rapidly. As more trials return, there is a need to look at the usage in all patients including those patients with kidney disease.

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