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REVIEW

Current treatment in COVID-19 disease: a rapid review

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Abstract

The world has faced the most challenging pandemic of the modern era, that of severe acute respiratory syndrome coronavirus 2 infection, causing coronavirus disease and affecting over 35 million people globally. The wide range of clinical manifestations associated with this viral disease is thought to be related to the overexpression of inflammatory markers. Due to a dysregulated host response, the most severe form involves multi-organ failure and thromboembolic complications. Immunomodulatory therapies may help prevent its progression and anticoagulation has been shown to reduce the risk of thrombotic complications. As this is a new entity for the medical world, there are no known therapeutic options nor has the prevention of complications been established. Anti-inflammatory agents, antimicrobial therapy, and vitamin supplements are short of clear benefits, but there is limited data to review. Other agents, such as convalescent plasma, eculizumab, immunoglobulins, neutralizing IgG1 monoclonal antibodies, remdesivir, steroids, and tocilizumab, have shown a possible impact on inpatient length of stay and mortality rate. This review aims to assess the efficacy and safety of these available therapies in light of current evidence. We compare these treatment options based on their impact on symptom management, inpatient length of stay, and overall morbidity and mortality.

Keywords: convalescent plasma, COVID-19, eculizumab, immunoglobulins, neutralizing IgG1 monoclonal antibodies, remdesivir, SARS-CoV-2, steroids, tocilizumab.

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Introduction

The world is facing the most challenging pandemic of the modern era, that of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, causing coronavirus disease (COVID-19), which has affected over 35 million people worldwide. This condition has been shown to be related to the overexpression of inflammatory markers, including interleukins. The widespread inflammatory dysregulated host response can result in multi-organ failure, thromboembolism and death.[1,2] Immunomodulatory agents and systemic anticoagulation might be useful to prevent disease progression and thromboembolic complications if initiated in selected groups of severely ill patients.[3] Here, we review various options that are available for the management of this condition using multiple sources, including journals, electronic libraries, and university portals. Our goal is to assist healthcare workers engaged in this ongoing pandemic to guide their management with this rapid and concise review.

Methods

We performed a retrospective analysis of 41 prominent original studies along with a review of widely published literature in medical journals regarding the available treatment options for COVID-19 infection in the period March to November 2020. These studies were reviewed after a cautious selection from university portals, multiple journals, and libraries, including but not limited to Nebraska University Library, *medRxiv*, *European Review for Medical and Pharmacological Sciences*, *Journal of Medical Virology*, *Science Translational Medicine*, HCA Lung Biological Network, *Journal of Thrombosis and Hemostasis*, *Journal of Thrombosis and Thrombolysis*, *Lancet Respiratory Medicine*, *JAMA*, *NEJM*, *Journal of the American College of Cardiology*, *Journal of the American Heart Association*, *Journal of Heart Failure*, *Chest*, *BMJ*, Levy Library (Icahn School of Medicine), PubMed, Medscape, and EBSCO host. The search was performed using the following keywords: SARS, SARS-CoV-2, COVID-19, coronavirus, virus, virology, COVID-19

treatment, SARS-CoV-2 treatment, SARS treatment, remdesivir, plasma, convalescent plasma, antivirals, azithromycin, oseltamivir, enoxaparin, heparin, apixaban, NOAC, ACE-inhibitor, angiotensin receptor blocker, chloroquine, hydroxychloroquine, vitamin D, vitamin C, eculizumab, immunoglobulins, tocilizumab, steroids, dexamethasone and methylprednisolone.

Discussion

Role of anti-inflammatory agents including steroids and tocilizumab

Several studies suggest that the cytokine release syndrome or 'cytokine storm', the release of IL-1, IL-6, IL-12, and IL-18 along with TNFα, as well as other inflammatory mediators play an important role in the clinical manifestations of COVID-19 infection.[4–7]

SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) located on the target cells in the respiratory system leading to activation of the SARS-CoV-2 S protein.[8,9] This results in a further activation of the inflammatory cascade. In patients with SARS-CoV-2 infection, the postmortem pathology has revealed tissue necrosis as well as macrophage and monocyte infiltrations in the gastrointestinal mucosa, heart, and lung tissues. Severe lymphopaenia with hyperactivated pro-inflammatory T cells and decreased regulatory T cells are commonly seen in critically ill patients, suggesting the importance of using immunosuppressive therapy to control the overactivated cytokine release syndrome.[10–12] Like other viral entities, profound lymphopaenia may also be present when the virus infects and destroys T cells. This mechanism includes both the adaptive and innate immune responses (comprising cell-mediated and humoral immunity), impairing lymphopoiesis and increasing lymphocyte apoptosis. Later, the virus replicates faster, compromising the endothelial–epithelial barrier, increasing the inflammatory response, and triggering the influx of monocytes and neutrophils.

Drugs such as tocilizumab work by binding to the cell-related and soluble IL-6 receptors, inhibiting classic signalling and trans-signalling, which results in improved outcomes of patients with significant pneumonia.[13,14] A single dose of tocilizumab 400 mg improved lung function in 91% of patients and decreased the length of hospitalization in a large single-centre trial.[15] Another small study demonstrated the usefulness of repeated doses in severely ill patients, although the sample size in the study was not significant.[16]

During the initial phase of the pandemic, a vast majority of patients received systemic steroids due to the established evidence of the efficacy of steroid use in systemic inflammatory response syndrome and patients mechanically ventilated due to respiratory illness. Multiple studies showed some benefit of steroid use, including a decrease in mortality, as observed in a trial at the University of Oxford including 6000 patients receiving 6 mg of dexamethasone daily.[17] The study showed a lower risk of death amongst the ventilated patients (rate ratio (RR) 0.65) and other patients receiving oxygen therapy (RR 0.80). Furthermore, the RECOVERY trial found that dexamethasone reduced 28-day all-cause mortality (21.6% *versus* 24.6%; age-adjusted rate ratio 0.83, 95% CI 0.74–0.92; $p<0.001$). Based on emerging data, dexamethasone is recommended in hypoxic patients but shows no difference in the routine use for mild disease manifestations.[18,19]

There are ongoing trials to evaluate the efficacy of using neutralizing antibodies (Abs) in patients with mild to moderate disease. The BLAZE-1 randomized, double-blind clinical trial by Eli Lilly and Company was designed to assess the efficacy and safety of LY-CoV555 (bamlanivimab) and LY-CoV016. The investigators showed that LY-CoV555 improved viral clearance at an earlier time point (3 days) when compared to placebo as well as the rate of hospitalizations and emergency room visits (1.7% (5/302) for LY-CoV555 *versus* 6% (9/150) for placebo, 72% risk reduction). The mechanism of LY-CoV555 is based on the neutralization of the IgG1 monoclonal Ab against the spike protein of SARS-CoV-2. It inhibits the viral attachment and entry into human cells, thus offering the possibility of treating and even preventing disease progression to a severe form.[20] REGN-COV2 is a combination of two monoclonal Abs, casirivimab (REGN10933) and imdevimab (REGN10987), being investigated by Regeneron Pharmaceuticals, Inc. in phases I–III randomized clinical trials in non-hospitalized patients with mild to moderate COVID-19. This investigational Ab cocktail was granted emergency use authorization due to a decrement in viraemia and the time to alleviation of symptoms.[21] Further follow-up on the final results of this treatment modality in ongoing randomized clinical trials is required.

Role of immunomodulatory agents and convalescent plasma transfusion

During the pandemics of the Spanish and Avian influenza in 1918 and 1996, respectively, significant benefits were noted with the use of convalescent plasma (CP) and immunoglobulin (Ig) infusions.[22–24] These therapies showed decreased morbidity, improved hospital length of stay, as well as a decrease in mechanical ventilation and mortality. Based on the usefulness during prior pandemics, these treatment modalities were evaluated for their efficacy in the management of COVID-19 infection. As noted in a recent publication by Rojas et al.,[25] the neutralization of the Abs, including the procoagulative reaction, was noted in patients who received CP or Ig infusions. In a trial headed by the Mayo Clinic for COVID-19 disease, CP was used in approximately 100,000 hospitalized patients (52% of these patients were in the intensive care unit (ICU) and 27% required mechanical ventilation) with moderate to severe illness in more than 2780 institutions.[26] The trial demonstrated that the use of CP with higher Ab levels was associated with reduced 30-day

mortality. The side-effects identified were allergy, haemolytic reactions, volume overload, and transfusion-related reactions, including transfusion-related acute lung injury. The authors noted a reduced morbidity and mortality in patients who received CP, but the effective dose still remains unknown. Furthermore, Zhang et al. discussed the positive effect of CP decreasing the autoimmune Abs (e.g. antiphospholipid, systemic lupus erythematosus, etc.) which elevation of and their decreased levels after the administration of CP.[27] In a recent study conducted at the Center for Infectious Disease Research and Policy, Van Beusekom showed no clear benefit of CP.[28] Additionally, Casadevall et al.[29] posed the question of monotherapy with CP and discussed a potential use in combination with antiviral drugs. In terms of Ig, numerous case reports, case series, and small studies have been published but do not offer an established conclusion in favour of Ig infusions.[30–33] However, most of the studies have shown a possible lead-time bias in terms of reliable outcomes.

Eculizumab is monoclonal Ab targeted against complement C5. Clinical improvement is related to the prevention of membrane attack complex formation, resulting in the avoidance of end-organ damage and possibly of microthrombi phenomenon.[34] In other studies, patients received eculizumab (off-label), enoxaparin 4000 IU daily, lopinavir 800 mg daily with ritonavir 200 mg daily, hydroxychloroquine 400 mg daily, ceftriaxone 2 g daily intravenously, and vitamin C 6 g daily for 4 days and were on non-invasive ventilation, showing a potential benefit in terms of recovery, duration of the disease, and decrease in inflammatory markers.[35,36]

In summary, our review of the literature showed a lack of evidence for routine use of Ig, CP, or eculizumab, but the selected treatment modalities can be useful in a specific patient population based on the severity of disease presentation. The individualization of treatment options and close monitoring of outcomes are a must, particularly as the long-term effects of these treatment options are unknown.

Role of systemic anticoagulation

In severe forms of COVID-19 infection, activation of the coagulation cascade and consumption of clotting factors occurs. Reports from Wuhan, China, indicated that up to 71% of patients who died met the criteria for diffuse intravascular coagulation.[37] Inflammation of the lung tissue and dysfunction of its endothelium may lead to a microthrombic phenomenon causing deep venous thrombosis, pulmonary embolism, and thrombotic arterial complications (e.g. limb ischaemia, ischaemic stroke, myocardial infarction). Prolonged thromboprophylaxis must be individualized based on risk *versus* benefit. In a retrospective analysis of a nationwide survey published in *BMJ*, low-molecular-weight heparin (LMWH) was associated with a decrease in overall 28-day mortality compared to subcutaneous mini-heparin (40% *versus* 64.2%).[38] The anti-inflammatory benefits of LMWH are related to its positive outcomes. Warfarin and direct-oral anticoagulants are not the drugs of choice due to the hepatic dysfunction present in severe illness, which leads to unpredictable levels in serum.[39–41]

Based on the review of the literature, we recommend prophylactic systemic anticoagulation to all patients who have no contraindication (no active bleeding). Subcutaneous LMWH is the preferred agent for prophylactic anticoagulation but, in patients with renal failure, apixaban can be considered. Patients with clinical or radiographic signs of clotting should receive a therapeutic form of anticoagulation (preferred agent subcutaneous LWMH). Whenever possible, mechanical thromboembolism prophylaxis should be considered if a clinical contraindication for system anticoagulation exists.

Role of antiviral agents including remdesivir

Antiviral drugs are thought to work in different phases of viraemia, including in the prevention of viral entry into the host cell and in the prevention of both viral activation and replication. Remdesivir works by inhibiting viral replication via an adenosine analogue that becomes incorporated into the viral RNA, resulting in the inhibition of further viral replication and in early termination of the viral cycle. Sheahan et al. showed a potential reduction in viral load and lung infection in mice after the use of remdesivir.[42] In a recent study performed in North America, Europe, and Japan, clinical improvement was seen in 68% of patients with the use of remdesivir 200 mg i.v. first, followed by 100 mg daily to complete 10 days while diagnosed with COVID-19 disease. However, some evidence from clinical trials in China showed no such clinical benefit of remdesivir treatment and were terminated earlier due to an increased side-effect profile.[43] The uncertainty with the clinical benefit of remdesivir warrants more research and analysis before considering the widespread use of this drug.[44–46]

Another antiviral agent widely considered for COVID-19 treatment is oseltamivir. The results of most observational studies showed inconsistent data about possible benefits *versus* no benefit. The main possible benefit is directed to the decrease in the time of recovery (1 day), but this topic is still controversial due to the heterogenetic evidence that is available.

The latest evidence on the efficacy of these therapies is not very promising. The World Health Organization launched new interim results from the SOLIDARITY trial that did not show a difference in mortality with remdesivir, hydroxychloroquine, lopinavir/ritonavir, and interferon regimens.[47] It is important to mention that this trial included data from multiple countries.

Role of antibiotics, hydroxychloroquine, and RAS modulators

As discussed earlier, activation of the immune response to SARS-CoV-2 involves the binding of viral particles to ACE2 receptors.

Based on this mechanism of viremia, it was hypothesized that medications such as ACE inhibitors (ACEi) and angiotensin receptor blockers might lead to increased susceptibility to COVID-19 infections due to receptor upregulation. Observation studies evaluated this relationship, and evidence-based data did not show any association between ACEi/angiotensin receptor blockers and infection risk or hospital mortality.[48] In a large population-based study from Denmark, 4480 infected patients were compared based on prehospitalization use of ACEi, and no difference in mortality was noted.[49,50]

Chloroquine/hydroxychloroquine (CQ/HCQ) were used widely during the initial phase of the pandemic due to their ability to inhibit viral entry, prevent endocytosis, downregulate the immune system, and decrease the cytokine storm. However, early data from clinical trials in the inpatient setting have not demonstrated clear benefits. The meta-analysis from multiple randomized clinical trials showed that CQ/HCQ with or without azithromycin were ineffective and rather may have increased the risk of adverse events.[47] HCQ did not show benefit in terms of mortality (RR 1.0, 95% CI 1.0–1.2, I^2 0%, n=6 studies), ICU use or need for mechanical ventilation (RR 1.1, 95% CI 0.9–1.4, I^2 0%, n=3 studies), virological cure (RR 1.0, 95% CI 0.9–1.2, I^2=55%, n=5 studies), or disease exacerbation (RR 1.2, 95% CI 0.3–5.0, I^2=29%, n=3 studies). There is clear data showing that CQ/HCQ, with or without azithromycin, is indeed ineffective in treating COVID-19 disease or its exacerbation.[51,52]

Role of vitamins C and D

Vitamin C has gained interest in the management of COVID-19 due to its inherent anti-oxidative properties. There are ongoing clinical trials in various centres to evaluate the outcomes of early vitamin C treatment in patients with various clinical manifestations, but, currently, insufficient data establishing the use of vitamin C is available. Prior studies have shown the potential benefits of vitamin C supplementation in the management of acute respiratory distress syndrome and septic shock due to other viral illnesses.[53] It is prudent to follow-up on the outcomes of current ongoing trials to guide therapy in particular for COVID-19 infection.[54]

There is growing interest to suggest that vitamin D deficiency is related to the risk of infection. This vitamin acts as an immune system modulator by providing an effective physical barrier and strengthening both adaptive and innate immunity. A meta-analysis of 25 randomized clinical trials in the past suggests that regular supplementation with vitamin D2/D3 (up to 2000 IU/d) is protective against acute respiratory infections.[55] Therefore, the prophylactic use of vitamin D in patients with COVID-19 is proposed. There is a lack of clinical data to support this treatment modality, and further clinical studies are needed to establish vitamin D supplementation as part of therapy.[56]

Tables 1 and 2 briefly summarize the current clinical trials on the treatment of COVID-19 infection.

Post-COVID-19 disease

Important signs or symptoms that follow acute infection are pain, physical competence, renal function, hypercoagulability, impaired renal function, myopathy or polyneuropathy, residual pulmonary infections, psychiatric or psychological disorders (anxiety, cognitive disorder, depression, insomnia, post-traumatic stress disorder), and cardiac

Table 1. Current treatment in COVID-19 infection.

Tocilizumab	The IL-6-mediated immune hyper-response in COVID-19 was assocated to poor outcomes. Small, retrospective studies suggest that elevated IL-6 levels may predict worse outcome in terms of morbidity and mortality. China has reported benefit of tocilizumab; however, when compared in multiple reviews, summary statements are inconclusive
Remdesivir	Effect against RNA viruses including SARS/MERS-CoV helps with early termination of the viral cycle
Plasma/ immunoglobulins	Related to decrease morbidity and duration of hospitalization and, in some cases, improved mortality
Dexamethasone	Related to reduced mortality and decrease in hospitalization length
Anticoagulation	Might decrease microthrombi formation
	Heparin was preferred due to its anti-inflammatory properties in view of the generalized inflammatory response, including lung tissue infection, in patients with COVID-19
Eculizumab	Inhibit membrane attack complex, possibly avoiding organ damage and the microthombi events
ACEi/ARB	Initially, theories were more in favour of discontinuation of ACEi/ARB therapy to decrease the risk of more severe COVID-19; however, multiple papers showed that these medications can be continued in COVID-19
	In terms of starting ACEi/ARB in COVID-19, data are inconclusive but most studies do not recommend their use
Oseltamivir	Coronaviruses do not utilize neuraminidase, and therefore, no activity is expected

Table 2. Clinical trials of current treatment in COVID-19 infection.

Remdesivir	ACTT-3 trial (NCT04492475)
Tocilizumab	COVACTA
	Tocilizumab clinical trials (NCT04315480 and NCT04306705)
	Wang M et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Research* 2020;30;269-271.
Convalscent plasma	Joyner MJ et al. Early safety indicators of COVID-19 convalescent plasma in 5000 patients. *J Clin Invest* 2020;Jun 11.
	Salazar E et al. Treatment of COVID-19 patients with convalescent plasma reveals a signal of significantly decreased mortality. *Am J Path* 2020;Aug 10.
	Joyner MJ et al. Effect of convalescent plasma on mortality among hospitalized patients with COVID-19: Initial three-month experience.
Dexamethasone	Hornby P et al. Effect of dexamethasone in hospitalized patients with COVID-19: Preliminary report.
	Villar J et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomized controlled trial.

manifestations, including arrhythmias and myocardial injury. Patients will therefore need to be closely monitored for chronic conditions, especially cardiovascular, metabolic, and neurologic disorders.[57,58]

Conclusion

The SARS-CoV-2 infection/COVID-19 is a pro-inflammatory process with multiple consequences, including an increased mortality rate, especially in patients with a medical history of heart failure, hypertension, or renal disease. Multiple data have shown the potential sequelae that patients might experience, including chronic fatigue, thrombotic events post infection, non-reversible lung disease, and altered mental and physical disability; however, these cannot yet be fully determined. Future studies following up on the cardiovascular, neurovascular, renal, and other potential complications that could result from this viral illness are warranted.

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