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Treatment options for patients with severe COVID-19

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Abstract: The coronavirus disease 2019 (COVID-19) pandemic has affected the world for over 3 years. Treatment options have improved substantially during this period, including antiviral drugs, antibody drugs, immune-based agents, and vaccination. While these improvements have reduced mortality rates in patients with COVID-19, some patients still develop severe illness. In this review, we aimed to provide an overview of treatments for patients with severe COVID-19 from study reports and clinical experience. We discussed the treatments from two perspectives: respiratory care and drug treatments. In the respiratory care section, we discussed the usefulness of high-flow nasal cannula therapy and non-invasive ventilation as an alternative to invasive ventilation. In the drug treatments section, we focused on three classes for severe COVID-19 treatment: antiviral drugs, immune-based agents, and anticoagulation therapy. We did not discuss antibody drugs and vaccination, as they are not used for severe COVID-19 treatment.

***Keywords*:** high-flow nasal cannula therapy, remdesivir, immune-based agents, anticoagulation therapy

Introduction

Since the first case of coronavirus disease 2019 (COVID-19) was reported in the city of Wuhan, China, at the end of 2019, the COVID-19 outbreak has continued for over 3 years. During this pandemic, there have been more than 700 million confirmed cases and six million deaths globally (*1*). Despite the challenges posed by this pandemic, the development of effective vaccines has reduced the incidence of severe COVID-19, hospitalizations, and mortality rates (*2*). Nevertheless, older patients or patients with underlying medical conditions remain vulnerable to severe or critical illness and death.

In this review, we summarized the treatment options for patients with severe COVID-19. Severe illness is defined by the International Diseases Society of America (IDSA) as patients with $SpO_2 \leq 94\%$ on room air, including patients on supplemental oxygen (*3*). In Japan, COVID-19 severity is classified into four categories; mild, moderate I, moderate II, and severe by the Ministry of Health and Welfare. The IDSA's definition of severe illness is equivalent to the moderate II and severe categories in Japan, and patients with moderate illness can easily progress to severe illness. Thus, we focused on treatments for patients receiving supplemental oxygen, which is a similar condition to patients with severe illness according to IDSA's definition.

Respiratory care

High-flow nasal cannula therapy (HFNC)

In acute respiratory failure, HFNC reportedly reduces intubation by 15% compared to conventional oxygen therapy (*4,5*). The usefulness of HFNC in patients with COVID-19 is discussed in several case series (*6-9*). Demoule *et al*. reported that HFNC reduced the intubation rate at day 28 compared to conventional oxygen therapy (55% *vs*. 72%; $p < 0.0001$) (*6*). Other studies have also suggested that with close monitoring, HFNC can be an effective tool (*7*). Another advantage of HFNC is that patients on HFNC can easily adapt a prone position. In patients with COVID-19, a prone position has been suggested to reduce intubation risk (*10*), which is consistent with non-COVID-19 acute respiratory distress syndrome (ARDS) (*11,12*). However, a concern is that HFNC may delay intubation resulting in poor prognosis. Kang *et al*. demonstrated that early intubation (within 48 h HFNC initiation) was associated with lower overall intensive care unit (ICU) mortality than late intubation (*13*). Therefore, Roca *et al*. suggested the ROX index as a tool to predict HFNC failure (*14*). Although it might be difficult to implement this index in all hospitals, close monitoring is necessary after HFNC initiation.

Nosocomial infections are another concern when using HFNC. The risk of droplet dispersion, aerosol generation, or infection transmission reportedly depends on the conditions of HFNC use (*5*). Properly fitted HFNC masks and the wearing of surgical masks by patients can

improve the situation (*15-17*). In our hospital, Katsuno *et al*. reported that half of the patients on HFNC (8/15 cases) were treated successfully, and no nosocomial infections occurred (*18*).

In conclusion, with adequate use and close monitoring, HFNC may play an important role in reducing the number of patients with COVID-19 who require invasive mechanical ventilation.

Non-invasive ventilation (NIV)

NIV is another alternative to intubation in hypoxic conditions (*19,20*). However, NIV effectiveness in ARDS is controversial due to high mortality and intubation rates (*21*). The guidelines do not recommend NIV use in ARDS (*22*). In COVID-19 cases, results vary depending on the study (*23-26*), and nosocomial infections also play a role in avoiding COVID-19 treatment with NIV. Moreover, Frat *et al*. reported that in immunocompromised patients, NIV had a higher risk of mortality and intubation than HFNC (*27*). There is no solid evidence to support or reject the use of NIV in COVID-19 treatment. More rigorous studies are needed to determine its efficacy; however, NIV may be considered an alternative to intubation in COVID-19 treatment.

Invasive mechanical ventilation

For patients with poor oxygen status, invasive mechanical ventilation is unavoidable. The COVID-19 mortality in patients on invasive mechanical ventilation was initially reported to be 88% (*28*). However, this figure excluded the patients who continued the treatment in the ICU. With advances in treatments, the mortality rates range from 26–39% (*29-33*). This data is consistent with ARDS without COVID-19 (*21*) and is not much worse than previous respiratory pandemics (*34*).

Intubation timing is controversial. Some studies support early intubation (*35,36*), whereas others have revealed no relationship between intubation timing and mortality (*37,38*). However, Riera *et al*. revealed that in later periods of the pandemic, the rate of early intubation diminished (*35*), indicating that clinicians increasingly chose to treat patients non-invasively. Therefore, while this issue remains controversial, we can conclude that with close monitoring, HFNC and NIV treatment could play an important role in avoiding intubation.

Drug treatments

There are three major options for treating patients with severe COVID-19: antiviral drugs, immune-based agents, and anticoagulation therapy.

Antiviral drugs

Remdesivir

Remdesivir is an antiviral drug that inhibits the RNA-dependent SARS-CoV-2 RNA polymerase and perturbs viral replication (*39,40*). Four randomized cotrolled trials (RCTs) have discussed the effectiveness of remdesivir in patients with severe COVID-19 (*41-44*), with varying results. Wang *et al*. reported a trial on remdesivir in 237 patients; however, it was underpowered based on the stringent public health measures in China (*41*). However, in a subgroup of patients observed within 10 days from symptom onset, patients on remdesivir demonstrated faster clinical improvement. The DisCoVeRy trial (*42*) and SOLIDARITY trial (*43*) also revealed negative results for remdesivir in severe cases.

In contrast, the ACTT-1 trial (*44*), which included 85% of patients with severe illness, reported positive results. The primary outcome was the time to recovery, and patients on remdesivir had a median recovery time of 10 days, compared to 15 days in the placebo group (rate ratio for recovery, 1.29; 95% confidence interval (CI,) 1.12–1.49; $p < 0.001$, based on a log-rank test). The difference in results could be due to the difference in patients' condition, oxygen demand, and outcome assessment methods. However, several studies have demonstrated a consistent trend toward the prevention of severe disease. In the ACTT-1 trial, among the 573 patients without NIV, high-flow oxygen, invasive ventilation, or extracorporeal membrane oxygenation (ECMO) at baseline, the incidence of new NIV or high-flow oxygen use was lower in the remdesivir group than in the placebo group (17% [95% CI, 13–22] *vs*. 24% [95% CI, 19–30]) (*44*). In the DisCoVeRy trial, among patients without mechanical ventilation or ECMO at randomization, remdesivir significantly delayed the need for new mechanical ventilation or ECMO or death (HR 0.66 (95% CI, 0.47–0.91), $p = 0.01$). Moreover, in the SIMPLE-2 study, patients with moderate COVID-19 treated with remdesivir revealed a better clinical status on day 11 compared to the placebo group (*45*).

These findings suggest that remdesivir may improve clinical outcomes for moderate disease or patients with early-stage COVID-19. In summary, remdesivir may prevent severe illness in patients with COVID-19 requiring oxygen. It is key to initiate remdesivir in the early stage. Moreover, the National Institute of Health recommends the treatment of hospitalized patients requiring oxygen with remdesivir but does not recommend remdesivir for patients requiring mechanical ventilation (*46*).

Immune-based agents

Corticosteroids

Corticosteroids are believed to modulate the excessive immune response to COVID-19 (*47*). They have been widely used for COVID-19 treatment; however, their use remains controversial (*48,49*). The RECOVERY trial (*50*) revealed the effect of dexamethasone in

addition to standard care. The primary outcome was 28-day mortality; 22.9% in the dexamethasone group and 25.7% in the control group died within 28 days (age-adjusted rate ratio, 0.83; 95% CI, 0.75–0.93; $p < 0.001$). In the subgroup of patients on invasive mechanical ventilation and patients on oxygen, the mortality incidence was lower in the dexamethasone group than in the usual care group. However, there was no significant difference in the subgroup without oxygen treatment. Moreover, seven RCTs revealed the effectiveness of corticosteroids in severely/critically ill patients (*51*), and IDSA recommends corticosteroids only for patients who require oxygen (*3*).

However, the duration and dosage of corticosteroids are controversial. Regarding the duration, long-term corticosteroid use may be a risk factor for prolonged COVID-19 infection (*52*). We reported a case of prolonged COVID-19 infection with non-Hodgkin lymphoma treated with rituximab. In our case, corticosteroids were administered for more than 100 days, and after the reduction of corticosteroids, the PCR test became negative, which indicates the possibility that corticosteroids prolonged the COVID-19 infection.

Regarding corticosteroid dosage, some studies discussed prednisolone pulse therapy for patients with COVID-19. The effect of prednisolone pulse therapy is controversial, and the results depend on the studies. Salvarani *et al*. reported no significant difference was observed in time to discharge between the prednisolone pulse group and the standard care group (*53*). However, no side effects were increased in the pulse group; thus, Salvarani *et al*. concluded that prednisolone pulse may be beneficial in some severe cases.

In summary, corticosteroids moderate the immune response to COVID-19 and improve mortality in severe cases. However, the appropriate dose and duration of corticosteroids should be elucidated in future studies.

IL-6 inhibitors (tocilizumab)

IL-6 is one of the cytokines that cause acute inflammation and cytokines storm in patients with COVID-19 (*54*). Tocilizumab is a monoclonal antibody that binds to IL-6 receptors and inhibits IL-6-mediated signaling (*55*). Many case series and observational studies have revealed the effectiveness of tocilizumab in patients with COVID-19 (*56-58*). Ten RCTs (*59-68*) have been conducted, and three of them (EMPACTA, REMAP-CAP, and RECOVERY) met the primary endpoints. However, varying results have been reported; there are two reasons for this. First, most of the enrolled patients were severely ill; however, the mortality in control groups ranged from 5–30%, and each study included patients from various backgrounds (*69*). The REMAP-CAP and RECOVERY trials included mostly severely ill patients and demonstrated the effectiveness of tocilizumab. They concluded that in severely ill patients, tocilizumab had a higher tendency to be effective than in moderately ill patients. Second, corticosteroids were used simultaneously. The percentage of patients treated with corticosteroids differed among the trials, ranging from 4% to 88% (*70*). In the RECOVERY trial (*66*), the effect on 28-day mortality was reported only in the subgroup with corticosteroids.

In the subgroup without corticosteroids, no significant difference was observed in 28-day mortality (rate ratio, 1.16; 95% CI, 0.91–1.48), hospital discharge (rate ratio, 0.98; 95% CI, 0.79–1.22), and invasive mechanical ventilation or death (rate ratio, 0.99; 95% CI, 0.82–1.18). The World Health Organization (WHO) REACT working group also reported in a meta-analysis that the odds ratio for the association of IL-6 antagonist treatment with 28-day mortality was 0.77 (95% CI, 0.68–0.87) and 1.06 (95% CI, 0.85–1.33) in the subgroup on corticosteroids and without corticosteroids, respectively (*71*). This result suggests that the effect of tocilizumab is apparent only with corticosteroids and is consistent with the RECOVERY trial. Based on these studies, WHO recommends combined treatment with corticosteroids and IL-6 receptor blockers for patients with severe COVID-19 (*72*). Tocilizumab is an effective treatment in combination with corticosteroids.

Janus kinase (JAK) inhibitors (baricitinib)

Baricitinib is a JAK inhibitor that targets JAK1 and JAK2 (*73*). COVID-19 induces cytokine release syndrome, and many cytokines employ intracellular signaling pathways mediated by JAKs; therefore, JAK inhibitors moderate immune response to COVID-19 (*74*). In addition, baricitinib might interrupt virus entry into cells (*75,76*).

Three RCTs discussed the effect of baricitinib (*77*). The ACTT-2 trial analyzed the effect of baricitinib and remdesivir in 1,033 patients (*77*). The primary outcome was the time to recovery. Patients receiving baricitinib and remdesivir had a median time to recovery of 7 days, compared to 8 days for the patients on placebo and remdesivir (rate ratio for recovery, 1.16; 95% CI, 1.01–1.32; $p = 0.03$). In the subgroup analysis, patients on NIV or high-flow oxygen had the largest benefits. Other subgroups did not reveal statistical benefits. The COV-BARRIER trial evaluated the effect of baricitinib in combination with standard care (*78*). The study excluded patients on invasive mechanical ventilation or patients without oxygen therapy and enrolled 1,525 patients. The primary outcome was the percentage of patients with disease progression, defined as increased oxygen demand. No significant difference was observed in disease progression by day 28. However, in the baricitinib group, 28-day all-cause mortality was significantly lower than in the standard care group. The largest benefit was observed in patients with NIV or high-flow oxygen.

The RECOVERY trial was the third and largest trial and included 8,156 patients (*79*). By day 28, 514 of 4,148

patients (12%) in the baricitinib group and 546 of 4,008 patients (14%) in the usual care group had died (age-adjusted rate ratio, 0.87; 95% CI, 0.77–0.99; $p = 0.028$). This study also revealed that patients on NIV had the largest benefit. A meta-analysis (*79*) also revealed a 43% reduction in mortality with JAK inhibitors.

In conclusion, baricitinib may be recommended for use in severe to critically ill patients, especially with NIV or HFNC. WHO suggests the use of baricitinib, in combination with corticosteroids and IL-6 receptor inhibitors (*72*).

Anticoagulation therapy

A relationship between COVID-19 infection and thromboembolic diseases has been reported (*80-85*). Elevated D-dimer has been associated with lower mortality rates (*86*), and observational studies revealed that anticoagulation therapy improves survival rates in hospitalized patients (*87,88*). The choice of and dosage of anticoagulant is controversial (*89*). The INSPIRATION trial used enoxaparin (*90*), and the RAPID trial used heparin (*91*). In the INSPIRATION trial, an intermediate dose of enoxaparin (1 mg/kg) revealed no significant difference in mortality and bleeding events compared to the normal dose (40 mg daily) (*90*). The RAPID trial compared therapeutic and prophylactic doses of heparin; the therapeutic dose of heparin reduced all-cause mortality (*91*), although a larger study revealed contrary results in critically ill patients (*92*). The HEP-COVID trial compared the therapeutic dose of enoxaparin to that of heparin and revealed that enoxaparin significantly reduced all-cause mortality (*93*). It was concluded from the ACTION trial that there was insufficient evidence to support the use of oral anticoagulants in hospitalized patients (*94*).

In conclusion, it is difficult to determine which dosage and treatment should be used in patients with severe COVID-19; however, heparin or enoxaparin is recommended for hospitalized patients.

Conclusion

We reviewed the treatment options for patients with severe COVID-19. Regarding respiratory treatments, HFNC may be an effective alternative to intubation, under close monitoring and appropriate for preventing nosocomial infections. Regarding drug treatments, we recommended three treatments: antiviral drugs, immune-based agents, and anticoagulation therapy. Immune-based agents should be selected based on the illness severity and may be used as a single agent or in combination. We have reviewed several reports on different treatment options for severe COVID-19; however, there are insufficient studies on the choice, timing, and duration of treatments. Further confirmatory evidence is warranted.

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