Review Article

COVID-19 Treatment

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Abstract

The ongoing outbreak of COVID-19 has posed a great threat to public health. The various degree and dynamic of illness severity, together with the fact that only few drugs have been proven as an effective therapy has created critical challenges in disease management. Patients in acute viral phase usually present with upper respiratory tract and/or gastrointestinal illness, fever, and myalgia. Antiviral therapy might provide the greatest benefit in reducing disease progression in such patients with older age or significant comorbidities while immunomodulators are less likely to provide advantages. Patients in immune dysregulation phase usually present with pneumonia of different severity. Main treatment that showed survival benefit in severe to critical COVID-19 patients in this phase seems to be immunomodulators, especially corticosteroids. Anticoagulation also has an important role in such patients. High-quality clinical trials are needed to identify effective treatments in reducing disease progression and mortality.

Keywords: COVID-19, SARS-CoV-2, Treatment

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Introduction

Coronavirus disease 2019 (COVID-19) due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been rapidly spread worldwide since the first reported case in December 2019. As of 30 June 2021, over 180 million cases and nearly 4 million deaths have been reported. Although a large proportion of infected people would experience no or only mild illnesses, they can transmit the virus to vulnerable population groups including older adults and those with significant comorbidities. Morbidity and mortality rates are usually higher among the latter, which significantly affects the healthcare system. To control the disease burden, efforts have been accelerated to develop safe and effective novel and repurposed medicines against COVID-19. Despite this, only few treatments have been demonstrated in clinical trials to reduce disease progression and death. As the pandemic is ongoing, affordable, and effective treatments are utmost important for alleviating intensive care unit (ICU) strain, reducing deaths, and preventing collapse of the healthcare system.

COVID-19 patients can present with a variety of disease severity and clinical manifestation can be dynamic in individual patients, from asymptomatic to critical illness, according to phases of the disease. Acute viral phase occurs in first days of illness with high SARS-CoV-2 viral load presents in upper respiratory tract. In this phase, the illnesses are usually mild or moderate. Most infected younger adults without comorbidities had viral clearance and resolution or improving of disease after this phase. In others, the disease may progress into immune dysregulation phase, which occurs around the second week of illness.[1] Patients in this phase develop pneumonia and can manifest with moderate, severe, or critical illness. To yield the greatest benefits for patients, especially in resource-limited settings, therapeutic options should be personalized and provided according to the severity and phase of the disease.

This article provides an update on the current pharmacological treatment of COVID-19, including antiviral drugs, monoclonal antibody, immunomodulators, and anticoagulation. Management of COVID-19 patients stratified by disease severity will be discussed here. Discussion of supportive and respiratory care is beyond the scope of this article.

Mild COVID-19

Mild COVID-19 has been defined by the National Institutes of Health (NIH) of the United States as having symptoms of upper respiratory tract infection, gastrointestinal symptoms, or generalized symptoms such as fever and muscle pain without clinical manifestation of lower respiratory tract infection.[2] While most patients would have self-limited illness and need only supportive and symptomatic treatment, disease progression to immune dysregulation phase might be developed in patients with certain medical conditions. Patients over 60 years of age and those with comorbidities, such as chronic lung disease, chronic kidney disease, cardiovascular disease, cerebrovascular disease, uncontrolled diabetes mellitus, cirrhosis, obesity, and immunocompromised patients are at higher risk of disease progression.[3] The key points are to detect these risk factors, monitor these patients closely and promptly start appropriate therapy according to phase and severity of disease.

A wistful therapeutic option includes medications that are safe and effectively reduce disease progression in high-risk patients. Few medications have been shown in clinical studies to serve this purpose, including inhaled budesonide, antiviral drugs, and andrographolide. A phase 2, open-label, randomised controlled trial with 146 participants conducted in the United Kingdom demonstrated that early use of inhaled budesonide at a dose of 800 mg twice daily reduced the likelihood of disease deterioration and reduced time to clinical recovery for 1 day without negative effect on SARS-CoV-2 viral load.[4] Another large multicenter, open-label, randomised controlled trial with 4,700 participants found that inhaled budesonide therapy within 14 days of illness onset shortened time to recovery and marginally reduced hospital admission or mortality at 28 days in nonhospitalized patients at high risk for complications.[5]

There are some convincing data of antiviral therapy in mild COVID-19. Prospective clinical trials in China and retrospective observational studies in Thailand demonstrated that favipiravir, an oral RNA-dependent RNA polymerase (RdRp) inhibitor, shortened time to viral clearance and improved clinical manifestation in patients with mild to moderate COVID-19.[6-8] A systematic review and meta-analysis, including randomized controlled studies, before-after controlled studies, and observational

studies of patients with mild to moderate illness, found that favipiravir induced better viral clearance on day 7 of treatment albeit no different on day 14. Clinical improvement was significantly better in the favipiravir group on day 7 and 14.[9] Another systematic review and meta-analysis of 8 randomised controlled trials and 1 nonrandomised trial demonstrated significant clinical improvement in the favipiravir group. Viral clearance, requirement for oxygen therapy, ICU transfer, and mortality rate were not significantly different.[10] At present, the main antiviral drug in Thailand for mild COVID-19 patients with or without risk factors for severe disease is favipiravir, as recommended by the department of medical services.[3]

Molnupiravir, a novel broad-spectrum RdRp inhibitor, has been proved to be effective in reducing inflammation in lung tissue of hamsters infected with SARS-CoV-2.[11] A phase 1 human study revealed that the medication was well tolerated with few adverse events. The drug was well absorbed with plasma concentrations exceeding expected therapeutic level based on animal models.[12] A randomised, placebo-controlled, phase 2 trial of early treatment with molnupiravir within 7 days of symptoms onset showed that the treatment was effective in reducing nasopharyngeal viral load at both day 3 and 5.[13] Further randomised controlled trials of favipiravir and molnupiravir are ongoing.

Ivermectin, a repurposed medicine, has demonstrated antiviral activity against SARS-CoV-2 in vitro by inhibiting nuclear import of viral proteins, viral entry and replication. Ivermectin also exhibited various anti-inflammatory effects.[14] A recent meta-analysis of 15 clinical studies found that ivermectin reduced mortality compared with no ivermectin with moderate certainty of evidence, especially in mild to moderate COVID-19 patients, without proven benefit in reducing need for mechanical ventilation.[15] Another meta-analysis of 18 randomised controlled trial, which included mild to severe COVID-19 patients, demonstrated significantly reduction in mortality, time to recovery, and time to viral clearance in patients who were treated with ivermectin.[16]

There is still limited convincing evidence for andrographolide, an extraction of *Andrographis paniculata* (Fah talai jone), in treating mild COVID-19. A non-randomised clinical trial of 835 mild COVID-19 patients in Thailand demonstrated that patients who received andrographolide at a dose of 180 mg per day developed disease progression in 0.97%, compared to 14.64% in patients without the medication.[17] Further randomised controlled trials are needed to encourage the use of this inexpensive traditional herbal medicine.

The NIH guidelines panel recommends using one of anti-SARS-CoV-2 monoclonal antibodies (i.e., bamlanivimab plus etesevimab, casirivimab plus imdevimab, sotrovimab) as soon as possible and within 10 days of symptom onset in mild to moderate COVID-19 patients at high risk of disease progression based on randomised controlled trials showing reduction in hospitalization and mortality.[2] Real-world studies confirmed the effectiveness of this treatment in reducing emergency department visits or hospitalizations in high-risk ambulatory patients.[18-19] The monoclonal antibodies exhibited less activity against variants of concern, such as P.1 (Gamma) and B.1.351 (Beta) and are not available in Thailand at the time of this writing.[2]

Moderate COVID-19

Moderate COVID-19 is defined as clinical manifestation of lower respiratory tract infection, no signs of impending respiratory failure, oxygen saturation of 94% on room air, and pulmonary infiltrates $\leq 50\%$.[2] Remdesivir, an intravenous RdRp inhibitor, has demonstrated potent in vitro activity against SARS-CoV-2 and was well tolerated in clinical trials.[20] A multinational, randomised, controlled trial found that remdesivir shortened the time to recovery in hospitalized patients who had evidence of lower respiratory tract infection, with most pronounced benefit in the subgroup of patients who required low-flow oxygen supplement. Although the greatest mortality benefit was also demonstrated in the subgroup with low-flow oxygen supplement, there was no statistically significant difference in mortality in the entire study cohort.[21] According to the NIH guidelines, there is insufficient evidence to recommend the routine use of remdesivir in hospitalized patients who do not require supplemental oxygen, although this therapy may be appropriate in patients at high risk for disease progression.[2] Thai Ministry of public health guidelines recommend the use of remdesivir in patients who require high-flow oxygen therapy or noninvasive ventilation with fraction of inspired

oxygen of at least 0.6, patients who require invasive ventilation, pregnant women with pneumonia, and patients who cannot take oral drug or have absorption problem.[3]

Based on the available evidence from systematic reviews and meta-analyses including clinical trials of mild to moderate COVID-19 patients, early favipiravir therapy seems to improve clinical recovery.[9-10] There are still not enough convincing evidence that favipiravir could affect other important clinical outcomes such as reduction in the rate of oxygen supplement, intubation, ICU transfer, and mortality, as well as the time to viral clearance. These studies should be interpreted cautiously due to differences in patient population, disease severity, outcome definition, duration of illness before receiving treatment, dose and duration of favipiravir, and concomitant medication. Therefore, well-conducted large randomised, controlled trial on the aforementioned clinical outcomes are still needed.

Ivermectin might be a promising therapeutic option but a large, well-design randomised controlled trial would be needed before strong recommendation can be made.

Although dexamethasone did not demonstrate short-term survival benefit in patients who did not need oxygen supplement in the RECOVERY trial,[22] corticosteroids might offer benefit in reducing disease progression. Small retrospective observational studies in Pakistan and China found that non-severe, deteriorating patients who received short-term, low-dose corticosteroids, such as 20 mg per day of prednisolone for 7 days, had less likelihood of developing severe disease than patients without corticosteroids without negative effect to viral clearance.[23-25] This therapeutic option should be considered in moderate COVID-19 patients entering immune dysregulation phase with progressing disease, especially those with persistent fever, cough, shortness of breath, or multifocal/bilateral pulmonary infiltrates.

Secondary bacterial infections are uncommon in this patient group. Antimicrobial therapy should not be used unless there is evidence of bacterial infection.

Severe to critical COVID-19

Severe COVID-19 is defined as having oxygen saturation of < 94% on room air, respiratory rate of > 30 breaths/min, PaO_2/FiO_2 of < 300 mmHg, or lung infiltrates > 50%. Critical COVID-19 is defined as having respiratory failure, septic shock, and/or multiple organ dysfunction.[2] In addition to oxygen, respiratory, or hemodynamic support and closed monitoring, favipiravir or remdesivir should be started immediately. A multinational, double-blind, randomised, controlled trial of 1,062 hospitalized patients with COVID-19 pneumonia demonstrated significantly shorter time to clinical recovery in the remdesivir group than in the placebo group (median of 10 days vs. 15 days; $P < 0.001$). The median duration from symptom onset to randomization was 9 days and 23% of the patients received corticosteroids. In the subgroup analysis, significant difference in recovery rate ratio remained in the subgroup with symptom duration ≤ 10 days and the subgroup with low-flow oxygen therapy at enrollment. Although the mortality rate by day 29 was nonsignificantly lower among the remdesivir group (11.4% with remdesivir and 15.2% with placebo), a statistically significance was reached in the subgroup of 435 patients who required low-flow oxygen at baseline (4% vs. 12.7%; hazard ratio 0.30 [95%CI, 0.14 - 0.64]). In addition, among 573 patients who did not require noninvasive ventilation, high-flow oxygen therapy, invasive ventilation, or extracorporeal membrane oxygenation (ECMO) at baseline, the incidence of new use of noninvasive ventilation or high-flow oxygen therapy was lower in the remdesivir group (17% vs. 24%). Among the 766 patients who were not receiving invasive ventilation or ECMO at baseline, the incidence of new use of these interventions was lower in the remdesivir group (13% vs. 23%).[21] The NIH guidelines panel recommends using remdesivir for 5 to 10 days in patients who required supplemental oxygen.[2]

A retrospective study of 142 severe COVID-19 patients in Turkey found a tendency of decreased mortality and need for mechanical ventilation in favipiravir group, although not statistically significant.[26] An open-label, randomised, multicenter controlled trial of 236 moderate to severe COVID-19 patients in China found that favipiravir reduced time to relief for pyrexia and cough, compared with arbidol.[7] An open-label, randomised, multicenter controlled trial in Saudi

Arabia assigned 132 patients to the standard-of-care plus favipiravir and hydroxychloroquine group and 136 to the standard-of-care group. Most of the patients (90.15%) required supplemental oxygen and 88.6% received corticosteroids. Chest radiograph showed bilateral pulmonary infiltrates in 90.9% of patients. Mean duration since symptom onset is 5.96 days in the treatment group and 5.75 days in the control group. There was no significant difference in time to clinical recovery (9 days in the treatment group vs. 7 days in the control group; $P = 0.29$) and 28-day mortality (7.63% vs. 10.32%; $P = 0.45$).[27] Another open-label, randomised, multicenter controlled trial in Iran compared favipiravir and lopinavir/ritonavir therapy in addition to standard of care in 380 patients, which 26.5% received corticosteroids. The median oxygen saturation was 89%. Lung computed tomography findings revealed bilateral lesions in 89% of patients. The number of in-hospital mortality, ICU admission, intubation, as well as time to clinical recovery were not significantly different between the groups.[28] A systematic review and meta-analysis including 12 clinical trials comparing favipiravir therapy with standard of care among moderate to severe COVID-19 patients did not demonstrate significant difference in fatality rate and requirement for mechanical ventilation.[29] Physicians should consider that the use of favipiravir once the patient has severe illness might be too late to control the disease. One possible explanation is that the hyperinflammatory response to SARS-CoV-2 contributes to the illness and such patient might be benefited from corticosteroids rather than favipiravir. The key point is that favipiravir therapy seems to provide clinical benefits if used during the early viral replication phase, not in the immune dysregulation phase.

Corticosteroids play a key role in these patients, which immune dysregulation is the underlying pathophysiology. The RECOVERY trial found that intravenous dexamethasone at a daily dose of 6 mg for up to 10 days exhibited short-term survival benefit in severe and critical COVID-19 patients, with greatest benefit demonstrated among patients who were receiving invasive mechanical ventilation at randomization. The survival benefit was demonstrated in the subgroup of patients who received treatment more than 7 days since symptom onset but not among those who received treatment earlier. Among the patients who were not receiving invasive mechanical ventilation at baseline, dexamethasone significantly reduced need for invasive mechanical ventilation. Among those who were receiving invasive mechanical ventilation at baseline, the number of patients with successful cessation of invasive ventilation was significantly greater in the dexamethasone group. However, it should be noted that there was a trend of increasing mortality in the dexamethasone group among those who did not require oxygen therapy at baseline, albeit statistical significance was not reached.[22] In real-world practice, a significant proportion of patients experienced clinical deterioration despite being treated with corticosteroids at this dosage. Escalating to high-dose corticosteroids such as 12 to 20 mg per day of dexamethasone has halted the clinical progression and improved recovery in most patients. Nevertheless, high-risk patients such as elderly and obese patients, might still had clinical worsening. Methylprednisolone, which has exhibited superior bronchoalveolar penetration,[30] should be considered in this scenario. A randomized controlled trial in Iran found that intravenous methylprednisolone pulse at a dose of 250 mg per day for 3 days provided clinical improvement and survival benefit in severe COVID-19 patients with oxygen saturation of < 90% and elevated C-reactive protein (CRP) and interleukin (IL)-6.[31] In summary, type, dosage, and duration of corticosteroids should be individualized according to clinical parameters and inflammatory markers. Repeated courses of corticosteroids might be needed in cases with inadequate response or worsening after initial improvement. Blood glucose should be monitored and controlled because corticosteroid-induced hyperglycemia is common. Secondary bacterial infection should be monitored and appropriate antibiotics should be initiated based on clinical evidence.

There is accumulating evidence for the use of IL-6 inhibitors (i.e., tocilizumab) and Janus kinase inhibitors (i.e., baricitinib, tofacitinib) for severe to critical COVID-19. To date, tocilizumab is the most studied immunomodulator. These trial results must be interpreted with caution due to difference in study design, treatment regimen, patient population, phase of disease, and primary outcome. Although many randomised controlled trials evaluating tocilizumab have not found posi-

tive influence on clinical outcomes, EMPACTA, REMAP-CAP, and RECOVERY trial did found benefit on primary outcome (i.e., organ support or death).[32] In the RECOVERY trial, 4,116 patients with progressive COVID-19 were randomly assigned to receive tocilizumab or usual care. Eighty-two percent of the patients also received systemic corticosteroids. The median number of days since symptom onset was 9 in the tocilizumab group and 10 in the control group. Forty-five percent of the patients received low-flow oxygen and 41% received high-flow oxygen or noninvasive ventilation at randomization. The mean CRP was 143 and 144 mg/L in the tocilizumab and control group, respectively. Tocilizumab significantly reduced 28-day motality and patients in the tocilizumab group were more likely to be discharged alive within 28 days. New use of hemodialysis or hemofiltration was also less likely in the tocilizumab group. In the subgroup analysis, the effect of tocilizumab on 28-day mortality remained statistically significant in the patients who received the treatment within 7 days of symptom onset, those who were not receiving invasive ventilation or ECMO at baseline, and those with concomitant use of corticosteroids. Among those not receiving invasive ventilation at baseline, new use of this intervention or death was significantly lower in the tocilizumab group.[33] The aforementioned 3 positive trials included patients with severe to early critical illness. Patients in this phase might not reach the state of irreversible multiorgan failure, thus could benefit from interrupting the inflammatory signaling pathways. Using the agent too early or too late might not yield survival benefit.

Baricitinib is an orally administered inhibitor of Janus kinase (JAK) 1 and 2, which are enzymes that initiate signal transduction by a number of cytokines involving in hyperinflammatory response to SARS-CoV-2. Baricitinib may also decrease receptor-mediated viral endocytosis by inhibiting AP2-associated protein kinase-1.[34] A single-center retrospective study in Spain found that among 43 patients with severe COVID-19 patients who received baricitinib for a median of 6 days, overall survival was 100% at day 30 and day 60. Thirty-six (84%) patients also received corticosteroids.[35] A multinational, double-blind, randomised, controlled trial evaluated 1,033 moderate-to-severe COVID-19 patients who were assigned to received baricitinib (up to 14 days) plus remdesivir (up to 10 days) or placebo plus remdesivir. The median days from symptom onset to randomization was 8. The median time to recovery was significantly shorter in the baricitinib group than in the control group (7 days vs. 8 days). In the subgroup analysis, the significant difference in the time to recovery occurred among those who received high-flow oxygen or noninvasive ventilation at baseline (10 days vs. 18 days). The 28-day mortality rate was numerically lower in the baricitinib group than in the control group (5.1% vs. 7.8%), although the statistical significance was not reached. The difference in mortality was most apparent among those who required supplemental oxygen or noninvasive ventilation at baseline. Among those who did not require invasive ventilator or ECMO at enrollment, incidence of new use of these interventions was significantly lower in the baricitinib group.[36]

The NIH guidelines panel recommends using either baricitinib or tocilizumab in combination with dexamethasone in patients who have progressing respiratory decompen-sation and require high-flow oxygen therapy or mechanical ventilation and have marked increased inflammatory marker (i.e., CRP $\geq$ 75 mg/L).[2]

Growing evidence suggests that anticoagulation provides survival benefit in COVID-19 patients, especially those who have severe to critical illness, although there is no firm conclusion on the type and dose of anticoagulant.[37-43] A number of systematic reviews and meta-analyses were conducted to investigate this issue. The first systematic review and meta-analysis of 1 randomised controlled trial and 36 observational studies on different doses and types of anticoagulants demonstrated similar mortality between the overall anticoagulant group and the non-anticoagulant group. Prophylactic dose was associated with significantly lower mortality compared with non-anticoagulant and intermediate-to-therapeutic dose, while intermediate-to-therapeutic dose was associated with increased odds of major bleeding compared with prophylactic dose.[37] The second, including 29 retrospective studies, found that anticoagulant reduced in-hospital mortality in hospitalized COVID-19 patients, compared with no anticoagulant. In the comparison between the

therapeutic and prophylactic regimen, the former was associated with decreased mortality among ICU or severe patients, but not among all patients. Bleeding occurrence was also associated with the therapeutic regimen, but not with the prophylactic one.[38] The third, including 11 retrospective studies, found that the overall mortality of the hospitalized patients was significantly lower in the prophylactic/therapeutic dose group than in the non-anticoagulant group. The evidence of benefit was greatest among those with critical illness. There was no association between bleeding events and anticoagulation.[39] A multicenter, randomised controlled trial in Iran compared intermediate dose (1 mg/kg daily of enoxaparin) with prophylactic dose anticoagulant (40 mg daily of enoxaparin) in 562 COVID-19 patients admitted to ICU. Antiviral therapy with remdesivir or favipiravir, corticosteroids, and tocilizumab were given in 77%, 93%, and 13% of the patients, respectively. There were no significant differences in the all-cause mortality, venous or arterial thrombosis, ventilator-free days, ICU length of stay, and major bleeding between the groups.[40] A multicenter, randomised controlled trial in Brazil evaluating 615 hospitalized COVID-19 patients with elevated d-dimer also found no significant differences in the composite of time to death, duration of hospitalization, or duration of supplemental oxygen use, as well as cumulative mortality through 30 days between the patients who received therapeutic dose and those who received standard prophylactic or intermediate dose anticoagulant. It should be noted that 82% and 7% of the patients in this trial had moderate and severe disease at the enrollment, respectively.[41] A recent multinational, randomised controlled trial separately evaluated 2,231 non-ICU patients with moderate to severe illness and 1,103 ICU patients with critical illness. The patients were assigned to received either therapeutic dose heparin or low-to-intermediate prophylactic dose anticoagulant.[42-43] In the non-ICU cohort, therapeutic dose heparin significantly increased organ support-free days and survival without organ support at 28 days. The benefit was greater in the subgroup with high d-dimer (≥ 2 times the upper limit of normal) than in the subgroup with low d-dimer (< 2 times the upper limit of normal). The composite of major thrombotic event or death was also significantly lower among the therapeutic dose group. More major bleeding occurred in the therapeutic dose group (1.9% vs. 0.9%), albeit not statistically significant.[42] In the ICU cohort, the organ support-free days and the percentage of patients who survived to hospital discharge were similar between the groups, as well as the composite of major thrombotic event or death. The number of major bleeding event was numerically higher in the therapeutic dose group than in the prophylactic dose group (3.8% vs. 2.3%).[43] Based on dysregulated immune response induced by SAR-CoV-2 that lead to immunothrombosis and contribute to organ failure, anticoagulants might benefit the patients by intervening in the process of clot propagation of the pulmonary vasculature but physicians should consider type and dose of the anticoagulant on a case-by-case basis by weighing benefits and risks.

Discussion

Development of treatments against COVID-19 has been advanced since the beginning of the pandemic. Despite plentiful of literature on COVID-19 management, there are still areas of uncertainty with aspects of pharmacological therapy in specific patients, such as those with clinical worsening despite receiving available evidence-based treatment. Based on the pathogenesis that results from direct virus effects, immunopathology, and thrombosis, therapeutic strategies must be planned with right agents at the right time window. Safe and highly effective treatments for preventing disease progression and death in patients at high risk are urgently needed while this protracted battle has not come to an end yet.

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