CEP Clin Exp Pediatr Vol. 65, No. 8, 377-386, 2022
https://doi.org/10.3345/cep.2022.00458

Review Article

Therapeutics for the treatment of coronavirus disease 2019 in children and adolescents

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Coronavirus disease 2019 (COVID-19) is a mild to moderate respiratory illness in most children and adolescents, but a small proportion develop severe or critical illness. Although pediatric clinical trials for the treatment of COVID-19 are sparse, there are some available drugs for children and adolescents with severe COVID-19. This review summarizes clinical data focusing on antiviral agents and immunomodulators for COVID-19 treatment. Additionally, the current recommendations for therapeutics for children and adolescents with COVID-19 are discussed. Remdesivir is suggested for pediatric patients with COVID-19 in the following cases: children and adolescents with severe COVID-19 who need supplemental oxygen without mechanical ventilation; adolescents aged ≥12 years and weight of at least 40 kg with COVID-19 who do not require supplemental oxygen and are within 7 days of symptom onset and are at high risk of progression to severe illness. Nirmatrelvir/ritonavir is considered for adolescents aged ≥12 years and weighing at least 40 kg who do not require supplemental oxygen and are within 5 days of symptom onset and are at high risk of progression to severe disease. Corticosteroids are not recommended in children and adolescents with mild to moderate COVID-19. Corticosteroids are recommended in children and adolescents with severe to critical COVID-19.

Key words: COVID-19, Therapeutics, Child, Adolescent

Key message

- Children and adolescents with high risks for severe coronavirus disease 2019 (COVID-19) should be identified and proper treatment should be provided promptly according to the patient's condition.
- Remdesivir can be considered for pediatric patients of all ages with COVID-19 who have an emergent or increase in supplemental oxygen.
- The use of corticosteroids is not recommended for patients with nonsevere COVID-19. Corticosteroids are recommended in children and adolescents with severe and critical COVID-19.

Introduction

Coronavirus disease 2019 (COVID-19) in children and adolescents is less severe than in adults and leads to a relatively mild clinical course requiring no special treatment in most cases.[1)] However, some children and adolescents with COVID-19 may show a seriously ill clinical course, which may result in mortality.[2-4)] Currently, there is a lack of clinical studies on therapeutics for children and adolescents with COVID-19, and the limited number of studies that have been reported are based on the results of research involving adults.[1,5-9)]

This review summarizes the clinical data and recommendations for children and adolescents, focusing on antiviral drugs and immunomodulators among the COVID-19 treatment drugs several overseas guidelines currently recommend, with the aim of helping treat COVID-19 in children and adolescents.

Classification of disease severity

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is associated with various clinical features ranging from asymptomatic to serious disease. In clinical trials to evaluate therapeutics for COVID-19 treatment, the categories of disease severity are generally defined using respiratory support requirements. In most guidelines, the severity of COVID-19 is classified using oxygen saturation and the necessity of supplemental oxygen or mechanical ventilation. Additionally, rapid aggravation of the clinical condition, hemodynamic instability, septic shock, and multiorgan dysfunction must also be considered to evaluate the severity of infection. Table 1 shows the classification of COVID-19 severity as suggested by the World Health Organization (WHO),[9)] the Infectious Diseases Society of America (IDSA),[10)] the North American Pediatric Infectious Diseases Experts Panel,[5)] and the Australian National COVID-19 Clinical Evidence Taskforce.[1)]

In this review, we classify the severity of COVID-19 by the situations in Korea and the clinical guidelines of other countries

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Received: 15 March 2022, Revised: 26 May 2022, Accepted: 2 June 2022

Table 1. Definition of disease severity in patients with coronavirus disease 2019

	Mild	Moderate	Severe	Critical
WHO[9] (children/adolescents/adults	Nonsevere: absence of signs of severe or critical disease		SpO_2 < 90% on room air Respiratory rate >30 in adults Raised respiratory rate in children* Signs of severe respiratory distress	Requires life sustaining treatment Acute respiratory distress syndrome Sepsis Septic shock
IDSA[10] (adults)	Nonsevere: patients with SpO_2 >94% not requiring supplemental oxygen		Patients with SpO_2 ≤94% on room air, including patients on supplemental oxygen	Patients on mechanical ventilation and ECMO End organ dysfunction in sepsis/septic shock
North American Pediatric Infectious Diseases Experts Panel[5]	No new or increased supplemental oxygen requirement, with symptoms limited to the upper respiratory tract	No new or increased supplemental oxygen requirement, with symptoms involving the lower respiratory tract, or radiographic findings on chest x-ray	New or increase from baseline supplemental oxygen requirement without the need for new or increase in baseline noninvasive†/invasive mechanical ventilation	New or increased requirement for invasive or noninvasive mechanical ventilation, sepsis, or multiorgan failure Or rapidly worsening clinical trajectory that does not yet meet these criteria
Australia[1] (children/adolescents)	No supplemental oxygen required to maintain SpO_2 >92%	Requires low-flow oxygen (nasal prongs or mask) to maintain SpO_2 > 92%	Requires high-flow oxygen at 2 L/kg/min to maintain SpO_2 > 92%	Hemodynamically unstable without inotropic or vasopressor support Other organ failure Requires advanced modes of support to maintain oxygenation: high-flow nasal oxygen at > 2 L/kg/min‡, or noninvasive ventilation, or intubation and

WHO, World Health Organization; IDSA, Infectious Diseases Society of America; SpO_2, peripheral oxygen saturation; ECMO, extracorporeal membrane oxygenation.
*Respiratory rate: <2 months, ≥ 60/min; 2–11 months, ≥50/min; 1–5 years, ≥40/min. †Noninvasive mechanical ventilation: high-flow nasal canula, continuous positive airway pressure, or bilevel airway pressure. ‡Infants and neonates <4 kg may be managed on high-flow nasal cannula oxygen at 2–8 L/min irrespective of weight.

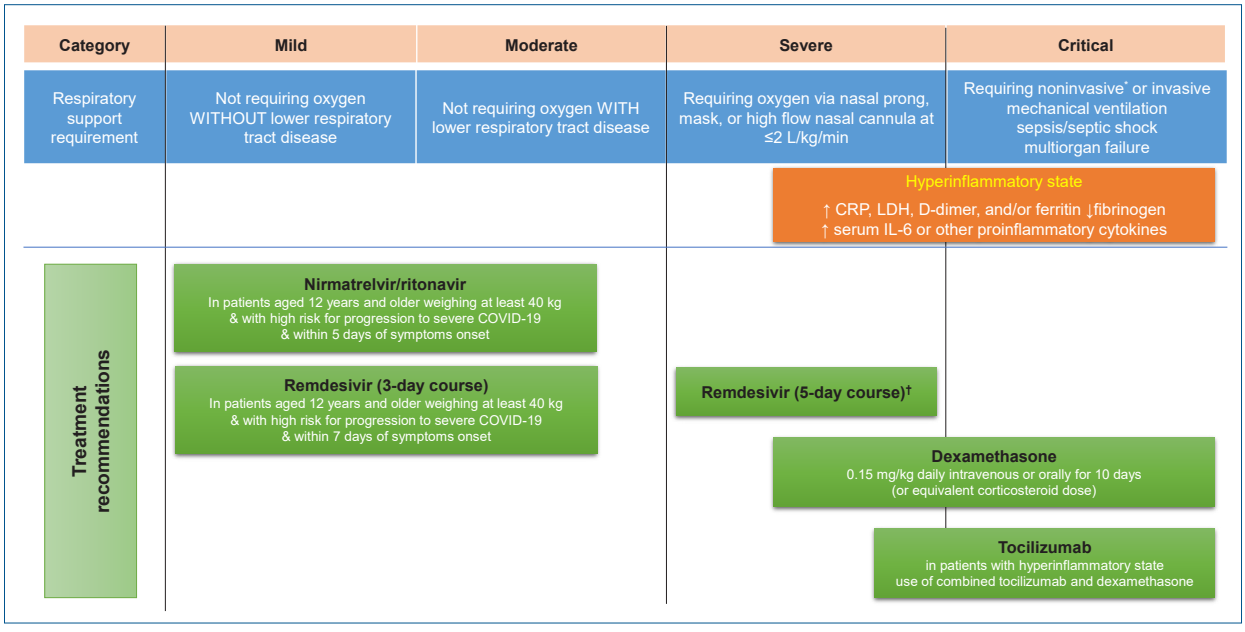

Fig. 1. Disease severity and treatment recommendations for children and adolescents with coronavirus disease 2019 (COVID-19). *Noninvasive mechanical ventilation: high-flow nasal canula at >2 L/kg/min oxygen, continuous positive airway pressure, or bilevel positive airway pressure. †In patients with pneumonia or on supplemental oxygen but not for those on mechanical ventilation or extracorporeal membrane oxygenation. CRP, C-reactive protein; LDH, lactate dehydrogenase; IL, interleukin.

and international organizations (Fig. 1). The severity of COVID-19 is defined as follows: mild - upper respiratory tract diseases without supplemental oxygen requirements; moderate - lower respiratory tract diseases not requiring supplemental oxygen; severe - lower respiratory tract diseases requiring oxygen via nasal prong, mask, or high-flow nasal cannula (HFNC) at ≤2 L/kg/min to maintain oxygenation; critical - COVID-19-related conditions requiring advanced modes of support (such as HFNC at >2 L/kg/min, mechanical ventilation, or extracorporeal membrane oxygenation [ECMO]), septic shock, or multiple organ dysfunction.

Antiviral agents

- Remdesivir is suggested for children and adolescents with severe COVID-19 or COVID-19 pneumonia who need supplemental oxygen without mechanical ventilation.
- Remdesivir is suggested for adolescents aged ≥12 years and weight of at least 40 kg with COVID-19 who do not need supplemental oxygen and are within 7 days of symptom onset and are at high risk of progression to severe disease.
- Nirmatrelvir/ritonavir is considered for adolescents aged ≥12 years and weighing at least 40 kg who do not require supplemental oxygen and are within 5 days of symptom onset and are at high risk of progression to severe disease.

1. Remdesivir

Remdesivir is a phosphoramidate prodrug that interferes with adenosine nucleotide analogues in cells.[11] Remdesivir binds to viral RNA-dependent RNA polymerase (RdRp) and inhibits viral replication through premature termination of RNA transcription. *In vitro* studies conducted before the COVID-19 pandemic have shown that remdesivir has antiviral effects on various RNA viruses, and clinical trials on the treatment of the Ebola virus have demonstrated the safety of remdesivir.

1) Clinical data

Most of the randomized clinical trials (RCTs) of remdesivir therapy in COVID-19 patients were conducted in adults, and there is a lack of studies involving children and adolescents.

The WHO Solidarity Therapeutics Trial was a multinational, open-label, adaptive RCT of repurposed drugs in hospitalized adult patients with COVID-19. In this study, 2,743 patients receiving a 10-day course of remdesivir and 2,708 receiving local standard of care were analyzed.[12] The mortality rate was 11.0% in remdesivir group and 11.2% in standard of care group; there was no significant difference between the 2 groups (rate ratio, 0.95; 95% confidence interval [CI], 0.81–1.11; P=0.50). The proportion of patients who initially did not but eventually required mechanical ventilation was 11.9% (295 of 2,489) and 11.5% (284 of 2,475) in remdesivir and standard of care groups, respectively.

The Adaptive COVID-19 Treatment Trial (ACTT-1), a multinational, placebo-controlled, double-blinded RCT of remdesivir in hospitalized adult patients with COVID-19 pneumonia. A total of 541 and 521 patients were assigned to the remdesivir and placebo groups, respectively, for 10-day treatment.[13] Remdesivir significantly shortened the recovery time (10 days vs. 15 days; rate ratio for recovery, 1.29; 95% CI, 1.12–1.49; P< 0.001). Furthermore, the benefit of remdesivir was the greatest in patients who were randomized within the first 10 days of symptom onset (rate ratio for recovery, 1.37; 95% CI, 1.14–1.64) and those who required supplemental oxygen therapy at the time of enrollment (rate ratio for recovery, 1.45; 95% CI, 1.18–1.79). However, there was no difference in time to recovery for patients who required high-flow oxygen therapy, noninvasive mechanical ventilation, mechanical ventilation, or ECMO. Patients in the remdesivir group were found to be more likely than those in the placebo group to have clinical improvement at day 15 (odds ratio [OR], 1.5; 95% CI, 1.2–1.9; P<0.001). The estimated mortality by day 29 was 11.4% in the remdesivir group and 15.2% in the placebo group, indicating no significant difference between the 2 groups (hazard ratio [HR], 0.73; 95% CI, 0.52–1.03). However, the subanalysis of the patients requiring supplemental oxygen therapy showed that the estimated mortality was 4.0% in the remdesivir group, which differed significantly from the 12.7% in the placebo group (HR, 0.30; 95% CI, 0.14–0.64). The proportion of serious adverse events was 25% in the remdesivir and 32% in the placebo group.

In a multinational, open-label RCT of the 5-day or 10-day remdesivir compared with standard of care in hospitalized adult patients with moderate COVID-19 pneumonia, patients in the 5-day remdesivir group had better clinical status on day 11 than those in standard of care group (OR, 1.65; 95% CI, 1.09–2.48; P=0.02); however, there was no difference between the 10-day remdesivir and standard care groups.[14] In another open-label RCT of adult patients with severe COVID-19 pneumonia, by day 14, clinical improvement of 2 points or more on the ordinal scale occurred in 64% of patients in the 5-day remdesivir group and in 54% in the 10-day remdesivir group. After adjustment for the baseline clinical status, there was no significant difference in the distribution of clinical status between the 2 groups at day 14. This study showed that in hospitalized adult patients with severe COVID-19 pneumonia who were not receiving mechanical ventilation or ECMO, using remdesivir for 5 or 10 days had similar clinical benefit.[15]

In a double-blind, placebo-controlled RCT of remdesivir for 3 days in nonhospitalized patients aged ≥12 years with COVID-19, patients who had symptom onset within the previous 7 days and who had at least one risk factor for disease progression (aged ≥60 years, obesity, certain coexisting medical conditions) were enrolled. The proportion of COVID-19-related hospitalization or death from any cause was 0.7% (2 of 279) in the 3-day remdesivir group, which differed significantly from the 5.3% (15 of 283) in the placebo group (HR, 0.13; 95% CI, 0.03–0.59; P=0.008).[16]

As of April 2022, there are no comparative clinical data evaluating the efficacy or safety of remdesivir in children and adolescents with COVID-19. However, there is an ongoing clinical trial to evaluate the safety, pharmacokinetics, and efficacy of remdesivir in children with COVID-19 under the age of 18 (ClinicalTrials.gov identifier: NCT04431453).[17] In the early stages of the pandemic, studies were conducted on the compassionate use of remdesivir in children and adolescents.[18,19] Goldman et al.[18] analyzed data from 77 patients from 6 countries who were administered remdesivir through the compassionate use program during the period March 21, 2020 to April 22, 2020. Approximately 79% (61 patients) of the participants had at least one underlying disease. Their median age was 14 years (interquartile range, 7–16 years), and 47% (36 patients) were

younger than age 12, including 4 patients under the age of 2 months. A total of 90% (69 patients) required supplemental oxygen, and 51% (39 patients) needed invasive mechanical ventilation. By day 28 of follow-up, 83% (64 patients) recovered, and 73% (56 patients) were discharged. In patients who required invasive mechanical ventilation, 67% (26 of 39) were discharged by day 28, and 13% (5 of 39) and 5% (2 of 39) did not require oxygen or required low-flow oxygen, respectively. Sixteen percent of patients (12 of 77) had any serious adverse events. Twenty-six (34%) had grade 3 or 4 elevations of serum creatinine levels (higher than 1.8 times the upper limit of normal) or transaminase levels (higher than 5 times the upper limit of normal).

2) Recommendations in the guidelines of other countries and international organizations

In the WHO living guideline, an initial conditional recommendation was made on November 20, 2020, suggesting not to use remdesivir for patients with COVID-19 regardless of illness severity. A new recommendation on using remdesivir for patients with nonsevere illness was published on April 22, 2022 (10th version). The WHO guidelines suggest treatment with remdesivir for patients with nonsevere COVID-19 at highest risk of hospitalization (conditional recommendation). Remdesivir should be administered as soon as possible after onset of symptoms, ideally within 7 days.[9)]

The Australian guidelines conditionally recommend the use of remdesivir in adult COVID-19 patients who require oxygen therapy but not mechanical ventilation.[20)] However, they recommend that the use of remdesivir in children and adolescents (under the age of 16) should not be routinely considered (conditional recommendation against).[1)]

The National Institute for Health Care and Excellence (NICE) recommends considering a 3-day course of remdesivir for adult or young people aged ≥12 years and weight of at least 40 kg with COVID-19 who do not supplemental oxygen and are within 7 days of symptom onset and are at high risk of progression to severe COVID-19 (conditional recommendation). A 5-day course of remdesivir is considered for adults or young people aged ≥12 years and weight of at least 40 kg who have COVID-19 pneumonia and are in hospital and need low-flow supplemental oxygen (oxygen delivered by a simple face mask or nasal cannula at a flow rate usually up to 15 L/min) (conditional recommendation).[7)]

The IDSA guidelines suggest that among patients with mild to moderate COVID-19 at high risk for progression to severe disease, a 3-day treatment with remdesivir is initiated within 7 days of symptom onset rather than no remdesivir (conditional recommendation). In patients on supplemental oxygen but not on mechanical ventilation or ECMO, the IDSA suggests remdesivir over no antiviral treatment and treatment with 5 days of remdesivir rather than 10 days of remdesivir (conditional recommendation). It is suggested against the routine initiation of remdesivir in patients with COVID-19 on invasive mechanical ventilation and/or ECMO.[10)] On April 25, 2022, the U.S. Food and Drug Administration (FDA) extended the approval of the use of remdesivir to include pediatric patients 28 days of age and older weighing at least 3 kg.[21)]

The National Institutes of Health (NIH) guidelines suggest that remdesivir can be considered for children of all ages with COVID-19 who have an emergent or increasing need for supplemental oxygen in consultation with a pediatric infectious specialist.[8)]

3) Considerations for administration

Remdesivir is available in 2 formulations for intravenous administration, a concentrated solution and a lyophilized powder. The concentrated solution should only be used in adults and pediatric patients weighing ≥40 kg, while the lyophilized powder can be used in adults and pediatric patients weighing ≥3 kg. Remdesivir contains the excipient sulfobutylether-beta-cyclodextrin sodium, which accumulates in patients with renal dysfunction. Remdesivir should not be administered to patients with an estimated glomerular filtration rate (eGFR) of less than 30 mL/min. Remdesivir is administered intravenously over 30–120 minutes. Remdesivir should be administered in a setting where severe hypersensitivity reactions, such as anaphylaxis, can be managed and the emergency medical system can be activated. Patients should be monitored during the infusion and observed for at least 1 hour after the infusion as clinically appropriate.[8)] During the treatment with remdesivir, liver function tests, renal function tests, and prothrombin time must be monitored. Remdesivir may need to be discontinued if a patient's alanine transaminase (ALT) level increases to >10 times the upper limit of normal, and it should be discontinued if increases in ALT levels and signs or symptoms of liver inflammation are observed.[8)]

The recommended dose for persons weighing between 3 kg and 40 kg is 5 mg/kg/dose on the first day, followed by 2.5 mg/kg/dose once daily on subsequent days. For those weighing over 40 kg, the recommendation is 200 mg on the first day, followed by 100 mg once daily on subsequent days.[10,22)]

As of May 9, 2022, remdesivir is available for children and adolescents in Korea in following cases[23)]: (1) patients weighing at least 3.5 kg with COVID-19 pneumonia or severe COVID-19 requiring supplemental oxygen therapy, excluding mechanical ventilation and/or ECMO; a 5-day treatment of remdesivir, and (2) patients aged ≥12 years and weight of at least 40 kg with mild to moderate COVID-19 who do not supplemental oxygen and are within 7 days of symptom onset and have at least one underlying medical conditions such as chronic lung disease, hypertension, cardiovascular or cerebrovascular disease, diabetes, obesity, active malignancy, immunosuppressive disease or receipt of immunosuppressive therapies, chronic kidney disease, chronic liver disease, or sickle cell disease; a 3-day treatment of remdesivir.

In July 2020, the Korean Ministry of Food and Drug Safety (MFDS) authorized the use of remdesivir for patients with COVID-19 weighing at least 3.5 kg who met the following

criteria: radiologically identified pneumonia (either by chest x-ray or computed tomography), oxygen saturation of less than 94%, and supplementary oxygen requirement. Based on the clinical trial data for remdesivir reported in other countries, on January 7, 2022, the Korean MFDS revised the approval of the use of remdesivir to limit hospitalized adults and adolescents aged ≥12 years and weight of at least 40 kg with COVID-19 pneumonia or severe COVID-19. However, since there were no antiviral drugs available for pediatric patients under 12 years of age in Korea, remdesivir was authorized for emergency use in these patients.[24] On January 20, 2022, the Korean MFDS also approved the emergency use of remdesivir in adults and adolescents with mild to moderate COVID-19 who are at high risk for progression to severe disease.[25]

2. Nirmatrelvir/ritonavir (Paxlovid)

Nirmatrelvir is orally bioavailable protease inhibitor that blocks viral replication by inhibiting Mpro (main protease), a cysteine protease of SARS-CoV-2. Nirmatrelvir is a substrate for cytochrome P450 3A4 (CYP3A4). Ritonavir, a HIV-1 protease, is a pharmacokinetic enhancer with no activity against SARS-CoV-2 Mpro. Ritonavir increases the plasma concentration of nirmatrelvir by inhibiting the CYP3A4-mediated metabolism of nirmatrelvir. Paxlovid (Pfizer, New York, USA) is co-packed with 300 mg of nirmatrelvir and 100 mg of ritonavir.[26]

The EPIC-HR (Evaluation of Protease Inhibition for Covid-19 in High-Risk Patients) study was a multinational randomized trial that compared the use of nirmatrelvir/ritonavir given orally twice daily for 5 days to placebo in nonhospitalized patients aged ≥18 years with mild to moderate COVID-19 who were at high risk of clinical progression. Eligible participants were randomized within 5 days of symptom onset, were unvaccinated against COVID-19, and had at least 1 risk factor for progression to severe disease. The incidence of COVID-19-related hospitalization or death by day 28 was lower in the nirmatrelvir/ritonavir group than in the placebo group by 5.62% points (95% CI, -7.21 to -4.03; $P<0.001$; relative risk reduction, 87.8%); the incidence was 0.77% (8 of 1,039 patients) in the nirmatrelvir/ritonavir group, with 0 deaths, as compared with 6.31% (66 of 1,039 patients) in the placebo group, with 12 deaths.[27]

On December 22, 2021, the FDA authorized the emergency use of Paxlovid for the treatment of patients with mild and moderate COVID-19 aged ≥12 years and weighing ≥40 kg who are within 5 days of symptom onset and at high risk of progression to severe disease, including hospitalization or mortality.[26] The IDSA guidelines suggest the initiation of nirmatrelvir/ritonavir within 5 days of symptom onset rather than no nirmatrelvir/ritonavir in ambulatory patients with mild to moderate COVID-19 at high risk for progression to severe disease (conditional recommendation).[19]

The WHO guidelines (10th version, updated on April 22, 2022) strongly recommend treatment with nirmatrelvir/ritonavir for patients with nonsevere COVID-19 at highest risk of hospitalization. Nirmatrelvir/ritonavir should be administered as soon as possible after onset of symptoms, ideally within 5 days. However, the strong recommendation in favor does not apply to pregnant women, children, or those with possible dangerous drug interactions.[9] The NICE guidelines recommend nirmatrelvir/ritonavir only for adult patients.[7]

The Australian guidelines recommend that nirmatrelvir/ritonavir is considered for treatment of COVID-19 within 5 days of symptom onset in children and adolescents aged 12 years and over and weighing at least 40 kg who do not require oxygen and who are at high risk of deterioration (pediatric complex chronic conditions, severe asthma, and obesity). The use of nirmatrelvir/ritonavir should be considered in children and adolescents who are not up-to-date with vaccination, or who are immunosuppressed regardless of vaccination status (consensus recommendation).[20]

Paxlovid is administered orally twice daily for 5 days. A single dose of nirmatrelvir/ritonavir is 300 mg/100 mg for patients with eGFR ≥60 mL/min and 150 mg/100 mg for patients with eGFR ≥30 to <60 mL/min. Nirmatrelvir/ritonavir is not recommended for patients with eGFR <30 mL/min.[26] Since nirmatrelvir/ritonavir interacts with many other drugs, the patients should be carefully assessed before administration. Nirmatrelvir/ritonavir should not be used with other drugs involved in CYP3A metabolism.

On December 27, 2021, the Korean MFDS authorized the emergency use of Paxlovid for the treatment of mild and moderate COVID-19 within 5 days of symptom onset. Paxlovid was first used in Korea on January 14, 2022. As of May 9, 2022, Paxlovid is available in patients aged ≥60 years, patients aged ≥40 years with underlying medical conditions such as diabetes, cardiovascular disease, chronic kidney disease, chronic lung disease, body mass index ≥30 kg/m^2, or neurodevelopmental disorders, and immunocompromised adolescents aged ≥12 years.[23]

3. Molnupiravir

Molnupiravir is a prodrug of β-D-N4-hydroxycytidine (NHC) that acts as a substrate for RdRp. NHC uptake by viral RdRp results in viral mutations (RNA mutagenesis) and subsequently inhibiting replication.[11,28]

MOVe-OUT was a multinational, phase 3 trial that evaluated the use of molnupiravir in nonhospitalized adults with mild to moderate COVID-19 who were at high risk of progressing to severe COVID-19. In the all-randomized modified intention-to-treat population, hospitalizations or deaths through day 29 had occurred in 48 of 709 participants (6.8%) in the molnupiravir group and in 68 of 699 participants (9.7%) in the placebo group (difference, -3.0 percentage points; 95% CI, -5.9 to -0.1).[29]

On December 23, 2021, the FDA authorized the emergency use of molnupiravir for the treatment of adults aged ≥18 years with mild and moderate COVID-19 at high risk of severe disease, including hospitalization or death.[30] The IDSA guidelines suggest the initiation of molnupiravir within 5 days of symptom onset rather than no molnupiravir in ambulatory patients

(≥18 years) with mild to moderate COVID-19 at high risk for progression to severe disease who have no other treatment options.[10] Molnupiravir is administered orally at 800 mg every 12 hours for 5 days, and dosage adjustment is not necessary in patients with kidney or hepatic impairment. Molnupiravir is not recommended for use in pregnant patients because fetal toxicity was reported in animal studies of molnupiravir. Molnupiravir is authorized for use in children aged <18 years due to its potential effects on bone and cartilage growth.[30]

As of May 9, 2022, in Korea, molnupiravir is available in patients aged ≥60 years, patients aged ≥40 years with underlying medical conditions such as diabetes, cardiovascular disease, chronic kidney disease, chronic lung disease, body mass index ≥30 kg/m^2, or neurodevelopmental disorders, and immunocompromised adolescents aged ≥18 years. Molnupiravir should be initiated within 5 days of symptom onset in patients with mild to moderate COVID-19 who have no other treatment options.[23]

Immunomodulators

- Corticosteroids are not recommended in children and adolescents with mild and moderate COVID-19.
- Corticosteroids are recommended in children and adolescents with severe and critical COVID-19, dexamethasone is administered orally or intravenously 0.15 mg/kg/dose (maximum dose 6 mg) once daily for up to 10 days.
- In children and adolescents with progressive severe and critical COVID-19 who have elevated markers of systemic inflammation, tocilizumab is considered in addition to dexamethasone.

1. Corticosteroids

Similar to other forms of severe viral pneumonia, excessive immune response is an important pathophysiology that aggravates COVID-19.[31] Therefore, steroids with strong anti-inflammatory and immunosuppressive effects have been suggested as one of the treatments for severe COVID-19.

1) Clinical data

Currently, there are no clinical data on the treatment of children and adolescents with COVID-19 using corticosteroids only. However, several RCTs involving adults showed that systemic corticosteroid therapy improved clinical outcomes and reduced mortality in hospitalized COVID-19 patients requiring supplemental oxygen therapy.[32-37] The RECOVERY trial is the largest multicenter, open-label RCT of dexamethasone in hospitalized patients with COVID-19 in the United Kingdom. A total of 6,425 patients underwent randomization; 2,104 received dexamethasone 6 mg intravenously or orally once daily plus standard care for up to 10 days or until discharge and 4,321 received standard care only.[36] The overall mortality rate at day 28 was 22.9% in the dexamethasone group and 25.7% in the standard care group (age-adjusted rate ratio, 0.83; 95% CI, 0.75–0.93; P<0.001). In patients with severe COVID-19 who required supplemental oxygen, dexamethasone reduce mortality at day 28, with greatest benefit in those with mechanical ventilation at randomization: patients requiring mechanical ventilation or ECMO at randomization, 29.3% in the dexamethasone group versus 41.4% in the standard care group (rate ratio, 0.64; 95% CI, 0.51–0.81); patients requiring supplemental oxygen but not mechanical ventilation at randomization, 23.3% in the dexamethasone group versus 26.2% in the standard care group (rate ratio, 0.82; 95% CI, 0.72–0.94). However, no survival benefit of dexamethasone who did not require supplemental oxygen at baseline (17.8% in the dexamethasone group vs. 14.0 % in the standard care group; rate ratio, 1.19; 95% CI, 0.92–1.55).

In the CoDEX (COVID-19-associated ARDS treated with DEXamethasone) trial, a multicenter, open-label RCT of dexamethasone in patients with acute respiratory distress syndrome (ARDS) in Brazil, patients who received mechanical ventilation within 48 hours of meeting criteria for moderate to severe ARDS were randomized to the dexamethasone group (20 mg intravenously daily for 5 days, then 10 mg for 5 days or until intensive care unit discharge; 151 patients) or the standard care group (148 patients).[35] Although the CoDEX trial was early terminated after the release of data from the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial, the mean number of days alive and free from mechanical ventilation by day 28 was significantly longer in the dexamethasone group (6.6 days in the dexamethasone group vs. 4.0 days in standard care group; P=0.04). Several RCTs of hydrocortisone[32] or methylprednisolone[37] in patients with severe COVID-19 showed the clinical benefits in the treatment failure or mortality rate. However, there were insufficient data to evaluate the efficacy of hydrocortisone and methylprednisolone because enrollment stopped after release of data from the RECOVERY trial.

2) Recommendations in the guidelines of other countries and international organizations

The WHO, IDSA, NIH, NICE, and Australian guidelines strongly recommend the use of corticosteroids in adult patients with severe and critical COVID-19 who require supplemental oxygen.[7-10,20] However, the use of corticosteroids is not recommended for patients with nonsevere COVID-19.

Although there is a lack of evidence for the use of corticosteroids in children and adolescents with severe COVID-19, several guidelines recommend the use of corticosteroids in pediatric patients with severe or critical COVID-19 based on clinical data from adult patients. The NIH guidelines recommend using dexamethasone for hospitalized children who require high-flow oxygen therapy, noninvasive ventilation, invasive mechanical ventilation, or ECMO.[22] The Australian guidelines recommend using dexamethasone daily intravenously or orally for up to 10 days (or acceptable alternative regimen) in children and adolescents with COVID-19 who are receiving oxygen

including those requiring mechanical ventilation (conditional recommendation).[1)]

3) Considerations for administration

Corticosteroids are not routinely recommended for pediatric patients who require only low levels of oxygen support but could be considered on a case-by-case basis. The use of dexamethasone for the treatment of severe COVID-19 in children who are profoundly immunocompromised has not been evaluated; therefore, such use should be considered only if the benefit is perceived to outweigh the risks.[8)] Dexamethasone is administered orally or intravenously 0.15 mg/kg/dose (maximum dose 6 mg) once daily for up to 10 days. If dexamethasone is unavailable, equivalent total daily doses of alternative corticosteroids may be used. Equivalent total daily doses of alternative corticosteroids to dexamethasone 6 mg daily are methylprednisolone 32 mg and prednisone 40 mg.[10)] During systemic corticosteroid administration, hyperglycemia, secondary infections, and risk of fungal opportunistic infection should be monitored.

2. Tocilizumab

Interleukin-6 (IL-6) is a pleiotropic cytokine produced by a number of nonhematopoietic cells and cells myeloid origin during infections and response to tissue damage. In some patients with COVID-19, a hyperinflammatory syndrome with elevated levels of proinflammatory cytokines and multiple organ dysfunction is observed.[6)] Elevated levels of blood IL-6, C-reactive protein (CRP), D-dimer, and ferritin are indicators of systemic inflammatory response related to COVID-19. Tocilizumab is an IL-6 receptor-inhibiting monoclonal antibody and has been suggested as a treatment for relieving hyperinflammation associated with COVID-19. Tocilizumab is authorized for the treatment of various rheumatic diseases and other immune disorders and is used in children aged ≥2 years. Tocilizumab is also used to treat severe cytokine release syndrome caused by chimeric antigen receptor T-cell treatment.[38)]

1) Clinical data

To date, there are no data from the clinical trials on tocilizumab treatment in children and adolescents with COVID-19. In the RECOVERY trial, severe COVID-19 patients with hypoxia (oxygen saturation <92% on room air or requiring oxygen therapy) and evidence of systemic inflammation (CRP≥75 mg/L) were eligible for random assignment in a 1:1 ratio to usual standard of care alone (2,094 participants) versus usual standard of care plus tocilizumab (2,022 participants).[39)] In the tocilizumab group, the 28-day all-cause mortality was significantly lower (31% vs. 35%; rate ratio, 0.85; 95% CI, 0.76–0.94; P=0.003). The proportion of patients discharged alive within 28 days was greater in the tocilizumab group (57%) than the usual care group (50%) (rate ratio, 1.22; 95% CI, 1.12–1.33; P<0.0001).

The WHO Rapid Evidence Appraisal for COVID-19 Therapies Working Group conducted a prospective meta-analysis to estimate the association between administration of IL-6 antagonists compared with usual care or placebo and 28-day all-cause mortality and other outcomes. In 19 trials that randomized 4,299 patients to tocilizumab (960 deaths) and 3,749 patients to usual care or placebo (1,023 deaths), compared with usual care or placebo, administration of tocilizumab was associated with lower 28-day all-cause mortality (OR, 0.83; 95% CI, 0.74–0.92; P<0.001). Concurrent administration of tocilizumab and corticosteroids was associated with lower mortality (OR, 0.77; 95% CI, 0.68–0.87). Secondary infections by 28 days occurred in 21.8% of patients treated with tocilizumab versus 19.2% of patients treated with usual care or placebo (OR, 0.95; 95% CI, 0.77–1.16).[40)]

2) Recommendations in the guidelines of other countries and international organizations

The WHO guidelines strongly recommend treatment with IL-6 receptor blockers such as tocilizumab or sarilumab for patients with severe and critical COVID-19. The WHO guidelines recommend patients meeting severe and critical severity criteria should receive both corticosteroids and IL-6 receptor blockers.[9)] Among hospitalized adults with progressive severe or critical COVID-19 who have elevated markers of systemic inflammation, the IDSA guidelines suggest tocilizumab in addition to standard of care (corticosteroids) rather than standard of care alone.[10)]

In the NIH guidelines, the position on the use of tocilizumab in pediatric patients with COVID-19 is undetermined due to insufficient evidence.[22)] On the other hand, the Australian guidelines conditionally recommend using tocilizumab in children and adolescents who require supplemental oxygen, particularly where there is evidence of systemic inflammation; the guidelines specify the use of combined tocilizumab and corticosteroids.[1)]

3) Considerations for administration

Administration of tocilizumab may cause serious and fatal infections (active tuberculosis, invasive fungal infection, and opportunistic bacterial, viral, or protozoan infections). Most of these infections are observed when other immunosuppressive agents are administered simultaneously. Therefore, prior to administering tocilizumab, the risks and benefits of treatment must be considered in patients with a history of chronic or recurrent infections.

The FDA has authorized the emergency use of tocilizumab in patients 2 years of age and older with COVID-19 who are receiving systemic corticosteroids and require supplemental oxygen, mechanical ventilation, or ECMO.[38)] The recommended dose and regimen are as follows: 12 mg/kg for persons weighing less than 30 kg and 8 mg/kg (maximum 800 mg) for persons weighing over 30 kg for a single intravenous administration over 60 minutes. If no clinical improvement is observed after the first administration, repeat dose may be administered every 8 hours for up to 3 additional doses. Tocilizumab administration is not recommended for patients with an absolute

neutrophil count of <1,000/mm^3, platelets <50,000/mm^3, or for those with active liver disease or hepatic insufficiency.[38]

3. Baricitinib: Janus kinase inhibitor

Janus kinase (JAK) inhibitors interfere with the phosphorylation of STAT (signal transducer and activator of transcription) proteins involved in important cellular functions, including signal transduction, growth, and survival. JAK inhibitors have been suggested as a treatment for COVID-19 due to their key functions of preventing the phosphorylation of key proteins involved in immune activation and signaling inflammation.[8]

Baricitinib is an oral JAK inhibitor that is selective for JAK1 and JAK2 and is currently used to treat rheumatoid arthritis. In the ACTT-2 trial, 1,033 adult patients hospitalized with COVID-19 were randomized 1:1 to receive baricitinib or placebo, both given in combination with remdesivir. Recovery time was shorter in the baricitinib group (7 days) than in the placebo group (8 days) (rate ratio for recovery, 1.16; 95% CI, 1.01–1.32; P=0.03).[41] In the COV-BARRIER trial, 1,525 hospitalized patients with COVID-19 pneumonia and an elevation in one or more inflammatory markers were randomized 1:1 to receive baricitinib or placebo.[42] The proportion of patients who progressed to high-flow oxygen, noninvasive ventilation, mechanical ventilation, or death by day 28 was 27.8% in baricitinib group versus 30.5% in the placebo group (OR, 0.85; 95% CI, 0.67–1.08). However, all-cause within 28 days was significantly different (8% vs. 13%; HR: 0.57; 95% CI, 0.41–0.78).

Several guidelines recommend administration of baricitinib in adult patients with severe or critical COVID-19. The WHO guidelines recommend that along with baricitinib, corticosteroids should also be administered in patients with severe or critical COVID-19. An IL-6 receptor blocker and baricitinib should not be given together and should be viewed as alternatives.[9] There are no recommendations for the use of baricitinib in children and adolescents. However, the FDA has authorized the emergency use of baricitinib in children and adult COVID-19 hospitalized patients aged ≥2 years who require supplemental oxygen, mechanical ventilation, or ECMO. The recommended dose is 2 mg once daily for children 2 to <9 years and 4 mg once daily for children ≥9 years. Duration of baricitinib is 14 days or until hospital discharge.[43] Baricitinib may increase the risk of serious infections that require hospitalization or can lead to death. Baricitinib is not recommended in patients with active tuberculosis and end-stage renal failure (eGFR<15 mL/min). In patients with an absolute lymphocyte count <200/mm^3 or an absolute neutrophil count <500/mm^3, baricitinib must be discontinued until recovery.[43]

Anti-SARS-CoV-2 monoclonal antibodies

SARS-CoV-2 monoclonal antibodies bind to the receptor-binding domain of spike proteins to exert effects. In clinical studies, SARS-CoV-2 monoclonal antibodies reduced hospitalization and mortality in patients with mild and moderate COVID-19 who had risk factors for progression to severe COVID-19.[44-47] Mak et al.[48] reported that monoclonal antibody treatment appeared to be safe and effective in some child and adolescent COVID-19 patients.

Among the SARS-CoV-2 monoclonal antibodies that the FDA has authorized for use, bamlanivimab/etesevimab, casirivimab/imdevimab, and sotrovimab can be administered to children and adolescents (Supplementary Table 1).[49] Bamlanivimab/etesevimab are the only SARS-CoV-2 monoclonal antibodies available for use in children under the age of 12.[50] However, a recent study found that several monoclonal antibodies had reduced effects against the omicron variant,[51] and because the omicron variant is currently the cause of the majority of COVID-19 cases, the FDA has restricted the use of bamlanivimab/etesevimab and casirivimab/imdevimab.[52]

Conclusion

Progression to severe and critical COVID-19 in children and adolescents is rare compared to adults. However, some children and adolescents with risk factors may develop severe and critical COVID-19. Children and adolescents with high risks for severe COVID-19 should be identified, and proper treatment should be provided promptly according to the patient's condition and with appropriate monitoring (Fig. 1).

Currently, clinical data on drug treatment for COVID-19 in children and adolescents is very limited. Recommendations in several guidelines are primarily based on the results of adult studies. Therefore, based on clinical data from pediatric studies, optimal evidence-based recommendations should be suggested to treat children and adolescents with COVID-19. Continuous interest in and the comprehensive acquisition of data related to the upcoming treatment of COVID-19 for children and adolescents are required.

Footnotes

Supplementary material: Supplementary Table 1 can be found via https://doi.org/10.3345/cep.2022.00458.

Conflicts of interest: No potential conflict of interest relevant to this article was reported.

Funding: This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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How to cite this article: Choi SH, Choi JH, Yun KW. Therapeutics for the treatment of coronavirus disease 2019 in children and adolescents. Clin Exp Pediatr 2022;65:377-86. https://doi.org/10.3345/cep.2022.00458